CLINICAL STUDY PROTOCOL

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Amendment No. 4 Final Version Date: 07 September 2021

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A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Crinecerfont (NBI-74788) in Adult Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment

Study No.: NBI-74788-CAH3003

EudraCT #: 2019-004873-17

NCT04490915

Development Phase: 3

Sponsor: Neurocrine Biosciences, Inc.
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SIGNATURES:

I agree to conduct the study in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Good Clinical Practices (GCP), and all applicable regulatory requirements.

CLINICAL STUDY TITLE: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Crinecerfont (NBI-74788) in Adult Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment

PROTOCOL No.: NBI-74788-CAH3003

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

CENTER:

_____

(Print Study Center Name)

Accepted for the Sponsor:

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2. SYNOPSIS

Title of study: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Crinecerfont (NBI-74788) in Adult Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment

Protocol number: NBI-74788-CAH3003

Phase of development: 3

Study center(s): Approximately 65 centers in the United States (US) and select ex-US countries

Objectives:

- To evaluate the efficacy of crinecerfont (100 mg twice daily [bid]), compared with placebo, in reducing daily glucocorticoid dosage while maintaining adrenal androgen control.
- To evaluate the efficacy of crinecerfont, compared with placebo, in reducing adrenal steroid levels following an initial 4-week treatment period.
- To evaluate the effect of crinecerfont, compared with placebo, on clinical endpoints associated with supraphysiologic glucocorticoid dosing.
- To evaluate plasma concentrations of crinecerfont and metabolites.
- To assess the safety and tolerability of crinecerfont.
- To evaluate an alternate dosing regimen of crinecerfont in subjects who have not reduced their glucocorticoid dose by Month 12.

Methodology:

This is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of crinecerfont versus placebo administered bid with breakfast and the evening meal (doses separated by approximately 12 hours) for 24 weeks in approximately 165 adult subjects with classic CAH due to 21-hydroxylase deficiency. Eligible subjects will be randomly assigned in a 2:1 ratio (active:placebo) to 2 treatment groups, crinecerfont 100 mg bid or placebo. After the 24-week randomized treatment period, there will be a 6 month, open-label treatment period, during which all subjects will receive crinecerfont 100 mg bid. At Month 12, subjects who have not reduced their glucocorticoid dose to ≤11 mg/m^2/day will be re-randomized (2:1) to receive 100 mg every morning (qAM) and 200 mg every evening (qPM) or to continue 100 mg bid, in a blinded fashion. Subjects who have reduced their glucocorticoid dose to ≤11 mg/m^2/day will continue to receive 100 mg bid in an open label fashion. At Month 18, subjects will review applicable portions of the informed consent form and confirm whether they will participate in the optional open-label extension (OLE) treatment period for continued access to crinecerfont.

During the OLE, subjects will have their glucocorticoid doses adjusted as appropriate and tolerated to achieve the lowest glucocorticoid dose that maintains adequate disease control (in the opinion of the investigator). The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents.

Starting at Month 18, all subjects who are continuing in the OLE will initially receive crinecerfont 100 mg bid. If the subject has inadequate disease control despite receiving glucocorticoid treatment at their target dose (in the opinion of the investigator), the crinecerfont dose may be increased to 100 mg qAM and 200 mg qPM. After the Month 24 visit, an alternative dosing regimen of once daily 200 mg qPM can be considered per the investigator.

Subjects will remain in the OLE until crinecerfont becomes commercially available, the Sponsor elects to discontinue development of crinecerfont for CAH, the Sponsor elects to discontinue the study, or the subject meets one of the study withdrawal criteria.

A final study visit will be conducted approximately 4 weeks after the last dose of study drug.

An independent Data Monitoring Committee (DMC) will periodically review ongoing clinical safety data to ensure the safety and well-being of study subjects. An interim analysis is planned after approximately 83 subjects (50% of planned sample size) have had the opportunity to complete the Week 24 assessments. At this time the primary endpoint will be evaluated for futility and unblinded sample size re-estimation based on the estimated treatment effect and the conditional power. The interim analysis will be performed using the "promising zone"

approach. The DMC will recommend one of the following actions: stop the study for futility, increase the sample size up to a maximum of 210 subjects, or continue the study as planned with no increase in sample size.

Screening period (Weeks -4 up to Day -1)

All subjects must provide signed and witnessed informed consent (which may be done remotely, if allowed and remote consenting procedures are in place) prior to the conduct of any study-related procedures. Subjects will undergo screening for up to 4 weeks (Weeks -4 to Day -1) to determine eligibility, with assessments performed according to the Schedule of Assessments. There will be a second visit (at home or the study site) during the screening period to collect a blood sample (for hormone measurements). The screening period may be extended by 2 weeks (if needed) for results of Screening Visit 2 hormone tests. Subjects must be on a supraphysiologic glucocorticoid regimen defined as >13 mg/m^2/day in hydrocortisone dose equivalents adjusted for body surface area (BSA) that has been stable at least 1 month leading up to screening. The glucocorticoid regimen should be optimized by the treating physician to achieve control of adrenal androgen levels and minimization of glucocorticoid dosage to the extent appropriate for the subject's individual medical needs and treatment goals.

Rescreening is permitted if a subject does not meet all eligibility requirements and returns to be rescreened. A subject that has failed screening twice may not be rescreened again without prior permission from the Medical Monitor.

Randomized, Double-Blind, Placebo-Controlled Treatment Period (Day 1 up to Week 24)

4-Week Glucocorticoid Stable Period (Day 1 up to Week 4)

During the first 4 weeks of the study, subjects should maintain their stable glucocorticoid regimen, except for sick-day guidelines. Sick-day dosing may follow guidelines outlined in Appendix B or will be based on guidance provided by the investigator or their treating physician.

On Day 1 (baseline), subjects will collect a urine sample (all voids from midnight the night before the study visit to the first morning void after awakening for the day) at home in the morning and bring it to the site for measurement of androgen metabolite levels. They will hold their morning glucocorticoid dose and bring it with them to the study site so that a blood sample can be obtained prior to taking the morning glucocorticoid dose; subjects will then take their morning dose of glucocorticoid at the study site, and another blood sample will be taken approximately 2 hours postdose in order to establish the baseline pre- and post-glucocorticoid hormone levels. Subjects should be fasting from the night before so that fasting blood tests and an oral glucose tolerance test can be performed, but should be encouraged to drink water to avoid any hypovolemic status.

Subjects will be randomized on Day 1 in a 2:1 ratio (active:placebo). Randomization will be stratified by total daily glucocorticoid dose, glucocorticoid type, and sex. Beginning on Day 1 (baseline), study drug will be administered at home with the subject's evening meal; thereafter, study drug will be administered bid with the subject's breakfast and evening meal (doses separated by approximately 12 hours).

8-Week Glucocorticoid Reduction Period (Week 4 up to Week 12)

During this period, subjects will undergo a down-titration (in 4 or fewer steps) of their glucocorticoid dose with the goal to reach a target dose of 8 to 10 mg/m^2/day (hydrocortisone equivalents adjusted for BSA) by Week 12, unless the subject has any signs or symptoms suggestive of clinically relevant glucocorticoid insufficiency or unacceptable symptoms of hyperandrogenism (see below for additional details on the glucocorticoid dose reduction schedule).

At the Week 4 visit, a similar procedure will be followed as for Day 1 to obtain a more detailed assessment of androgen status, with collection of a urine sample at home and collection of blood samples prior to and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. At this visit, the investigator will instruct the subject on the first step of the glucocorticoid dose reduction and arrange to contact the subject by telephone within a week of the study visit to assess how the subject is tolerating the glucocorticoid dose reduction. During the follow-up telephone contact, if the investigator feels that a clinical assessment and/or laboratory tests are needed, these can be performed as an unscheduled visit.

Subjects will have study visits at Weeks 6 (at home or the study site), 9 (at home or the study site), and 12 for study assessments, including collection of blood samples to assess hormone levels and routine safety assessments.

At the Week 6 visit, the investigator will instruct the subject on the second step of the glucocorticoid dose reduction (if applicable) and, if a glucocorticoid dose reduction occurred, will arrange to contact the subject by telephone within a week of the study visit to assess how the subject is tolerating the glucocorticoid dose

reduction. The investigator will contact the subject at approximately Week 8 to advise on the third step of glucocorticoid dose reduction (if applicable).

At the Week 9 study visit, the investigator will assess whether the subject is tolerating the third glucocorticoid dose reduction (if applicable). The investigator will contact the subject at approximately Week 10 to advise on the fourth step of glucocorticoid dose reduction (if applicable) and, if a glucocorticoid dose reduction occurred, will arrange to contact the subject by telephone within a week of the study visit to assess how the subject is tolerating the glucocorticoid dose reduction.

If the subject experiences any of the following signs or symptoms at any time during the glucocorticoid dose reduction process, the glucocorticoid dose should NOT be reduced further but returned to the previous dose that was tolerated. However, before the glucocorticoid dose reduction is stopped for symptoms or signs of orthostatic hypotension, volume status should be optimized (eg, with additional dietary salt, salt tablets, intravenous saline).

- Unexplained hyponatremia (serum sodium <135 mmol/L)
- Orthostatic hypotension with decrease in systolic blood pressure >20 mmHg or in diastolic blood pressure >10 mmHg after standing (from a seated position) after approximately 2 minutes, or severe symptoms of dizziness or lightheadedness upon standing
- Severe nausea, food aversion, vomiting
- Unacceptable symptoms of hyperandrogenism (eg, hirsutism, acne, amenorrhea)

Glucocorticoid dose reductions during Weeks 4 to 12 should proceed even if androstenedione levels increase transiently, provided that the increase is asymptomatic and tolerated by the subject.

At the Week 12 visit, based on review of the subject's hormone levels collected up to that visit as well as based on clinical assessment, the investigator will determine the appropriate dose of glucocorticoid to continue past Week 12 (the reduced dose if tolerated, or a prior [higher] dose) in order to achieve adequate control of androgen levels (ie, androstenedione ≤120% of the subject's baseline or ≤upper limit of normal [ULN] for age and sex).

12-Week Glucocorticoid Optimization Period (Week 12 up to Week 24)

Subjects will continue on the glucocorticoid regimen as instructed by the investigator at Week 12 and return to the study site at Week 16 (at home or the study site), Week 20 (at home or the study site), and Week 24 during the glucocorticoid optimization period. At these visits, the investigator will review the laboratory results from the preceding study visit and determine if the glucocorticoid regimen requires adjustment in order to achieve adequate control of androgen levels (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex).

At the Week 24 visit, subjects will follow a similar procedure as Day 1 for additional androgen assessments with collection of a urine sample at home and collection of blood samples prior to and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. Subjects should be fasting from the night before, but should be encouraged to drink water to avoid any hypovolemic status, and a glucose tolerance test will be performed (with study drug taken with the glucose load rather than a meal).

Open-Label Treatment Period (Week 24 up to Month 12)

For the purpose of this study, months are defined as 4-week intervals.

Starting the evening of the Week 24 visit (after all Week 24 assessments have been performed), all subjects will receive active study drug (crinecerfont) 100 mg bid with breakfast and evening meals. Subjects should continue the glucocorticoid regimen specified by the investigator at Week 24. Subjects and investigators will remain blinded to subjects' treatment group assignment from the double-blind period.

1-Month Glucocorticoid Stable Period (Week 24 up to Month 7)

During the first month of open-label treatment with crinecerfont, subjects should maintain a stable glucocorticoid regimen (except for sick-day guidelines).

3-Month Glucocorticoid Reduction Period (Month 7 up to Month 10)

At Months 7 (at home or the study site), 8, and 9 (at home or the study site), investigators will decrease glucocorticoid doses in those subjects whose glucocorticoid dose is still greater than 11 mg/m^2/day at Month 7 (unless there is a safety concern with regard to glucocorticoid insufficiency), with the goal to achieve a target physiologic dose of 8 to 10 mg/m^2/day by Month 10. The glucocorticoid dose should be reduced by approximately 10% to 20% at each visit (Months 7, 8, and 9), as long as androstenedione levels are controlled (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex) and the subject is not experiencing

any signs or symptoms suggestive of clinically relevant glucocorticoid insufficiency or unacceptable symptoms of hyperandrogenism. The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents. After each of the glucocorticoid dose reduction steps, the site should contact the subject by telephone (within a week) to assess how the subject is tolerating the glucocorticoid dose reduction. Subjects will have study visits at Months 8, 9, and 10 for study assessments including collection of blood samples for hormone levels.

2-Month Glucocorticoid Maintenance Period (Month 10 up to Month 12)

Subjects will have study assessments at Month 10 (at home or the study site) and Month 12 as outlined in the Schedule of Assessments. During this period, the goal should be to maintain stable glucocorticoid doses; however, the dose can be adjusted according to standard of care (eg, to achieve the control of androgen levels appropriate to the treatment targets for each subject).

At the Month 12 visit, subjects will have additional androgen assessments with collection of a urine sample at home and blood sample collection before and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. Subjects should be fasting from the night before (subjects should be encouraged to drink water to avoid any hypovolemic status). A glucose tolerance test will be performed (with study drug taken with the glucose load rather than a meal) at the Month 12 visit.

Open-Label or Double-Blind Active-Controlled Treatment (Month 12 to Month 18)

6-Month Glucocorticoid Maintenance Period (Month 12 to Month 18) for Subjects with Month 12 Glucocorticoid Dose ≤11 mg/m^2/day

Subjects with glucocorticoid dose ≤11 mg/m^2/day at Month 12 will continue on active study drug at 100 mg bid until Month 18 with study visits at Months 14 (at home or the study site), 16 (at home or the study site), and 18. The goal during this period is to maintain stable glucocorticoid doses while androstenedione levels are controlled (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex), although the dose can be adjusted according to standard of care.

At the Month 18 visit, subjects will have additional androgen assessments with collection of a urine sample at home and blood sample collection before and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. Subjects should be fasting from the night before (subjects should be encouraged to drink water to avoid any hypovolemic status).

6-Month Glucocorticoid Reduction/Optimization (Month 12 to Month 18) for Subjects with Month 12 Glucocorticoid Dose >11 mg/m^2/day

Subjects with glucocorticoid dose >11 mg/m^2/day at Month 12 will be re-randomized (2:1) to adjust active study drug dose to 100 mg qAM and 200 mg qPM or to continue active study drug at 100 mg bid; study drug will be blinded such that all re-randomized subjects will be taking the same number of capsules. Subjects should maintain a stable glucocorticoid regimen (except for sick-day guidelines) for the first month until the Month 13 visit. At the Month 13 visit, subjects will have additional androgen assessments with collection of a urine sample at home and blood sample collection before and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site.

At Months 13, 14 (at home or the study site), and 16 (at home or the study site), investigators will decrease glucocorticoid doses with the goal to achieve a target physiologic dose of 8 to 10 mg/m^2/day by Month 18. The glucocorticoid dose should be reduced by approximately 10% to 20% at Months 13, 14, and 16, as long as androstenedione levels are controlled (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex) and the subject is not experiencing any signs or symptoms suggestive of clinically relevant glucocorticoid insufficiency or unacceptable symptoms of hyperandrogenism. The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents. After each of the glucocorticoid dose reduction steps, the site should contact the subject by telephone (within a week) to assess how the subject is tolerating the glucocorticoid dose reduction.

At the Month 18 visit, subjects will have additional androgen assessments with collection of a urine sample at home and blood sample collection before and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. Subjects should be fasting from the night before (subjects should be encouraged to drink water to avoid any hypovolemic status).

Open-Label Extension (OLE) Treatment Period (Month 18 Onwards)

At Month 18, subjects will review applicable portions of the informed consent form and confirm whether they will participate in the optional OLE.

During the OLE, subjects will have their glucocorticoid doses adjusted as appropriate and tolerated to achieve the lowest glucocorticoid dose that maintains adequate disease control (in the opinion of the investigator). The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents. After each glucocorticoid dose reduction, the site should contact the subject by telephone (within a week) to assess how the subject is tolerating the glucocorticoid dose reduction.

Starting at Month 18, all subjects who are continuing in the OLE will initially receive open-label crinecerfont 100 mg bid. If the subject has inadequate disease control despite receiving glucocorticoid treatment at their target dose (in the opinion of the investigator), the crinecerfont dose may be increased to 100 mg qAM and 200 mg qPM (including at Month 18, after laboratory results are available). If the increased dose of 100 mg qAM and 200 mg qPM is not well tolerated, the dose may be reduced back to 100 mg bid. After the Month 24 visit, an alternative dosing regimen of once daily 200 mg qPM can be considered per the investigator. Crinecerfont doses should generally only be adjusted at or shortly after study visits (after laboratory results are available).

In the setting of inadequate disease control, if the glucocorticoid dose is at or above the target, an increase in the glucocorticoid dose should generally be considered only after the crinecerfont dose has been maximized for the subject. Changes to the glucocorticoid and crinecerfont doses should generally be separated by at least 1 month in order to assess the effect of each change.

Study visits during the OLE will occur every 3 months until Month 24, and every 6 months thereafter, with the option of having the Month 21 visit at home. At the Month 24 visit, and every 12 months thereafter, subjects will have blood sample collection before and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. Subjects should be fasting from the night before (subjects should be encouraged to drink water to avoid any hypovolemic status). A glucose tolerance test will also be performed at Month 24 and every 12 months thereafter (with study drug taken with the glucose load rather than a meal).

Subjects will remain in the OLE until crinecerfont becomes commercially available, the Sponsor elects to discontinue development of crinecerfont for CAH, the Sponsor elects to discontinue the study, or the subject meets one of the study withdrawal criteria.

Follow-Up Period

A final posttreatment visit will be conducted approximately 1 month after subject's final dose of study drug. This visit is not required if the subject transitions during the OLE to taking commercially-available crinecerfont or to another crinecerfont study.

Study Assessments and Study Visit Scheduling

Efficacy, safety, and PK will be assessed at scheduled times throughout the study. As much as possible, all study visits (including baseline and follow-up) should occur at approximately the same time in the morning to standardize time of day for assessment of efficacy, safety, and drug exposure.

In the double-blind, placebo-controlled portion of the study, all visits after Day 1 during the glucocorticoid stable period and glucocorticoid reduction period have a visit window of +5 days, and all visits during the glucocorticoid optimization period have a visit window of ±5 days. In the open-label treatment period, visits from Month 7 to Month 10 have a visit window of ±5 days and visits from Month 12 to Month 18 will have a visit window of ±7 days. During the OLE, visits will have a visit window of ±14 days. If a subject's glucocorticoid regimen is adjusted due to sick-day guidelines, the subject should resume their glucocorticoid dosing regimen for at least 3 days before their next scheduled hormone panel assessment, and this 3-day window supersedes all other visit windows.

Study population: Approximately 165 female and male subjects, at least 18 years of age, with a documented medical diagnosis of classic CAH due to 21-hydroxylase deficiency will be enrolled into this study.

Duration of treatment and study participation: The expected duration of study participation for each subject is approximately 20 months, plus a variable amount of time in the OLE (estimated average of approximately 24 months), including 1 month for screening, 6 months of blinded placebo-controlled treatment, 6 months of open-label treatment, 6 months of open-label or blinded active-controlled treatment, a variable amount of time of extension period treatment, and 1 month of follow up.

Investigational product, dosage and mode of administration: Crinecerfont 100 mg bid (200 mg total daily dose) administered in oral capsule form with subjects' breakfast and evening meal (doses separated by approximately 12 hours). Beginning at Month 12, crinecerfont may be administered as 100 mg qAM and 200 mg qPM (300 mg total daily dose). Each crinecerfont capsule contains 50 mg of crinecerfont (free base). Beginning at Month 18, crinecerfont doses will be 100 mg bid (200 mg total daily dose). During the OLE, crinecerfont doses may be increased to 100 mg qAM and 200 mg qPM (300 mg total daily dose) for inadequate disease control (including at Month 18, after laboratory results are available), or continued at 100 mg bid. Beginning at Month 24, at the discretion of the investigator, crinecerfont may be administered once daily as 200 mg qPM (200 mg total daily dose).

Reference therapy, dose and mode of administration, batch number: Matching placebo capsules are identical in appearance to crinecerfont and will be orally administered as needed to maintain the blind as required per applicable study period (ie, double-blind, placebo-controlled treatment period or double-blind, active-controlled treatment period).

Criteria for evaluation:

Efficacy:

Daily glucocorticoid regimen expressed in hydrocortisone equivalents adjusted for body surface area (BSA) (mg/m^2/day).

Hormone measurements: 17-hydroxyprogesterone (17-OHP) (serum; ng/dL), androstenedione (serum; ng/dL), testosterone (serum; ng/dL), adrenocorticotropic hormone (ACTH) (plasma; pg/mL), cortisol (serum; µg/dL), luteinizing hormone (LH) (serum; IU/L), follicle stimulating hormone (FSH) (serum; IU/L), progesterone (serum; ng/mL), plasma renin activity (measured upright) (ng/mL/hr).

Urine androgen metabolite levels (androsterone and etiocholanolone).

Metabolic assessments (fasting lipid panel, homeostatic model assessment of insulin resistance [HOMA-IR] based on fasting glucose and insulin levels, glycated hemoglobin [HbA1c], glucose tolerance test).

Dual-energy X-ray absorptiometry (DXA) scan (bone mineral density and body composition).

Blood pressure.

Hirsutism and Acne Scales (female subjects only).

Testicular ultrasounds (to detect adrenal rest tissue) (male subjects only).

Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).

Bone markers: serum osteocalcin, serum bone-specific alkaline phosphatase, serum C-terminal telopeptide, urine N-terminal telopeptide.

Patient-Reported Outcomes:

36-Item Short Form Health Survey (SF-36), EQ-5D-5L, Multidimensional Assessment of Fatigue (MAF), Psychological General Well-Being Index (PGWBI), and Medical Outcomes Study 12-Item Sleep Scale (MOS-12).

Pharmacokinetics:

Blood samples to evaluate plasma concentrations of crinecerfont and metabolites will be collected throughout the study.

Safety:

Safety and tolerability will be monitored throughout the study and will include the following assessments:

- Adverse events (including glucocorticoid-related events)
- Clinical laboratory tests
- Vital signs
- Weight/body mass index (BMI), and waist circumference
- Physical examinations
- 12-lead electrocardiograms
- Brief Psychiatric Rating Scale (BPRS)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical Considerations: The primary endpoint is the percent change from baseline in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for BSA [mg/m^2/day]) at Week 24, while Week 24 androstenedione is adequately controlled at ≤120% of baseline or ≤upper limit of normal for age and sex. An unblinded interim analysis will occur when approximately the first 83 subjects (approximately 50% of the planned number of enrolled subjects) have had the opportunity to complete the Week 24 assessments. The primary analysis of the primary endpoint will be performed using the weighted CHW (Cui, Hung, and Wang) test statistic comprising test statistics from stage 1 of the study (the interim dataset) and stage 2 of the study (final data set excluding subjects analyzed in the interim dataset). Each test statistic will be generated using an analysis of covariance (ANCOVA) model.

The first key secondary endpoint is the change from baseline in serum androstenedione at Week 4, which will be analyzed using an ANCOVA model.

The second key secondary endpoint is the achievement of a reduction in glucocorticoid daily dose to physiologic levels (≤11 mg/m^2/day in hydrocortisone equivalents adjusted for BSA) at Week 24 while controlling androstenedione levels (as defined above in the primary endpoint), which will be analyzed using a Cochran-Mantel-Haenszel (CMH) test.

Additional key secondary endpoints are the changes from baseline in HOMA-IR, weight, and fat mass at Week 24, which will be analyzed using an ANCOVA model.

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17-OHP	17-hydroxyprogesterone
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasm concentration versus time curve
AUC_{0-24}	AUC from time 0 to 24 hours
β-hCG	beta-human chorionic gonadotropin
bid	twice daily
BMI	body mass index
BPRS	Brief Psychiatric Rating Scale
BSA	body surface area
CAH	congenital adrenal hyperplasia
CFR	Code of Federal Regulations
CHW	Cui, Hung, and Wang
CMH	Cochran-Mantel-Haenszel
CI	confidence interval
C_{max}	maximum plasma concentration
CRF_1	corticotropin-releasing hormone receptor 1
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450 enzyme
DMC	Data Monitoring Committee
DSPV	Drug Safety and Pharmacovigilance
DXA	dual energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDTA K_2	dipotassium ethylenediaminetetraacetic acid
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
FAS	full analysis set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HbA1c	glycated hemoglobin
HOMA-IR	homeostatic model assessment of insulin resistance
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

INR	international normalized ratio
IRB	Institutional Review Board
ISC	Independent statistical center
IUD	Intrauterine device
IRT	Interactive response technology
LH	Luteinizing hormone
MAF	Multidimensional Assessment of Fatigue
MDD	major depressive disorder
MOS-12	Medical Outcomes Study 12-item Sleep Scale
NBI	Neurocrine Biosciences, Inc.
NOAEL	no observed adverse effect level
NTx	N-terminal telopeptide
OLE	Open-label extension
P-gp	P-glycoprotein
PGWBI	Psychological General Well-Being Index
PK	pharmacokinetics
PRA	plasma renin activity
PT	prothrombin time
qAM	every morning
qd	Once daily
qPM	every evening
QTcF	QT interval corrected for heart rate using Fridericia's correction
RAS	re-randomization analysis set
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SF-36	36-Item Short Form Health Survey
T4	thyroxine
TART	testicular adrenal rest tumor
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
UDS	Urine drug screen
ULN	upper limit of normal
US	United States
WBC	white blood cell

4. ETHICS

The sponsor personnel and the investigators will ensure that the study is conducted in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, and with the laws and regulations of the country in which the study is conducted.

The investigator and/or sponsor/Contract Research Organization (CRO) will submit this protocol and any related document(s) to be provided to the subject to an Independent Ethics Committee (IEC) / Institutional Review Board (IRB) and to the national competent (health) authority (as applicable). Approval documentation (as applicable) from both the IEC/IRB and the national competent (health) authority must be obtained before starting the study.

5. INTRODUCTION

5.1. Background

Crinecerfont is a selective corticotropin-releasing hormone receptor 1 (CRF_1) antagonist that is being developed as a novel oral treatment of congenital adrenal hyperplasia associated with high adrenocorticotropin and adrenal steroid insufficiency. One clinical manifestation of the absence of cortisol that occurs in congenital adrenal hyperplasia (CAH) is the lack of feedback inhibition of pituitary adrenocorticotropic hormone (ACTH) secretion. Increased ACTH levels cause adrenal hyperplasia and the enzyme block causes a shunting of cortisol precursor steroids to alternate pathways. Most notably, the shunting to androgens leads to virilization and other developmental complications in females, and the elevated ACTH levels are associated with the formation of testicular adrenal rest tumors (TARTs) in males. In addition, since the same enzyme (21-hydroxylase) is used in the pathway for the biosynthesis of the mineralocorticoids, a number of these patients suffer from aldosterone deficiency which can result in dehydration and death due to salt-wasting.

While survival is properly ensured through steroid replacement strategies based on physiologic dosing of glucocorticoids (eg, hydrocortisone) and mineralocorticoids (eg, fludrocortisone), these doses are often inadequate to suppress the overproduction of ACTH, progestogens, and androgens (eg, 17-hydroxyprogesterone [17-OHP], androstenedione, and testosterone). The uncontrolled symptoms of androgen excess, indeed, have a substantial impact on the day-to-day functioning and development of these patients. The glucocorticoid doses required to treat the androgen excess are typically well above the normal physiologic doses used for cortisol replacement alone (as in patients with Addison's disease). This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients (Elnecave et al., 2008; King et al., 2006; Migeon and Wisniewski, 2001).

Corticotropin-releasing factor is a hypothalamic hormone released directly into the hypophyseal portal vasculature and acts on specific CRF_1 receptors on corticotropes in the anterior pituitary to stimulate the release of ACTH. Blockade of these receptors has been shown to decrease the release of ACTH in both animals and humans. Therefore, compounds that block CRF_1 receptors have the potential to directly inhibit the excessive ACTH release that occurs in CAH and thereby allow for normalization of androgen production while using lower, more physiologic doses of

hydrocortisone. The novel CRF_1 receptor antagonist, crinecerfont, may provide an important therapeutic approach to treat patients with CAH.

5.2. Crinecerfont

The toxicity of crinecerfont has been assessed after oral administration following single and repeat dosing in the CD-1 mouse (up to 3 months), Sprague Dawley rat (up to 6 months), and Beagle dog (up to 12 months). No signs of acute toxicity were observed in rats following a single administration up to 2,000 mg/kg with the tosylate salt, and the maximal tolerated dose determined with the crinecerfont free base in rats was considered to be above 2,000 mg/kg. Additionally, crinecerfont was well tolerated in male dogs up to 1,500 mg/kg. In repeat-dose toxicity studies, the main target organs were liver (mouse, rat, and dog), coagulation parameters (rat only), thyroid gland (rat and dog), and gastrointestinal tract (mouse and rat). Repeat-dose nonclinical toxicology studies revealed no observed adverse effect level (NOAEL) of at least 15 mg/kg/day in the mouse, 5 mg/kg/day in the rat, and 1,000 mg/kg/day in the dog. These NOAEL doses yielded plasma exposures that were comparable or above the maximum expected human exposure. A fertility study was conducted in male and female rats. Oral administration of crinecerfont prior to and after cohabitation through a seminiferous cycle in male rats at doses of up to 1000 mg/kg/day had no effects on fertility, mating performance or gestation parameters. No developmental toxicity was observed up to 2,000 mg/kg/day in pregnant rats and up to 500 mg/kg/day in pregnant rabbits. Crinecerfont was negative in in vitro (Ames and mouse lymphoma) and in vivo (rat micronucleus test) genotoxicity assays. Results from these assays with crinecerfont showed no evidence of genotoxicity or clastogenicity. Based on these results, crinecerfont is assessed as being unlikely to have human teratogenicity/fetotoxicity potential in early pregnancy.

To date, crinecerfont has been administered to over 700 human subjects. A total of 363 healthy male and female subjects have been exposed to crinecerfont in 7 completed Phase 1 single-dose and 4 completed repeat-dose studies. Additionally, 361 male and female subjects with major depressive disorder (MDD) were exposed to crinecerfont (20, 50, and 100 mg) for up to 8 weeks in a Phase 2 active- (escitalopram) and placebo-controlled dose-finding study (DFI5687). After 14-day repeated oral administration of crinecerfont (20, 50, 100, and 200 mg as a free base, encapsulated lipidic formulation), crinecerfont AUC from 0 to 24 hours (AUC_{0-24}) increased slightly less than dose-proportionally (TDR10671). Steady state was reached after 7 days of treatment and the accumulation ratio was 1.44, suggesting that the effective half-life is approximately 14 hours. A long apparent terminal elimination phase half-life was observed with an overall mean value of 20.6 days across the dose range, which, in conjunction with the relatively low accumulation ratio, suggests that the terminal elimination phase is not a major contributing component to accumulation. After single oral administration of crinecerfont 20 mg or 50 mg with a moderate-fat breakfast, maximum plasma concentration (C_{max}) was increased by 3.8- and 2.6-fold, respectively, and AUC by 3.6- and 2.4-fold, respectively, compared to fasting conditions (TDU10479). In vitro metabolism studies indicate that crinecerfont is mainly metabolized by cytochrome P450 (CYP) 3A4 and CYP2B6. In vitro, crinecerfont was not a direct inhibitor of any CYP, with the exception for weak inhibition of CYP3A4; crinecerfont was also a weak time-dependent inhibitor of CYP3A4. Crinecerfont did not induce CYP1A2 gene expression or enzyme activity, but did cause a small increase in CYP2C9 and CYP3A4 gene expression concurrent with a concentration-related decrease in enzyme activity. Concomitant

administration of repeated 400 mg once daily (qd) of ketoconazole (14 days) with a single oral dose of 50 mg crinecerfont in healthy subjects resulted in a 1.25-fold increase in crinecerfont C_{max} and a 1.45-fold increase in crinecerfont AUC (INT5449). Concomitant administration of repeated 100 mg doses of crinecerfont (8 days) with single oral doses of midazolam in healthy subjects slightly increased the AUC of midazolam compared to baseline: 1.23-fold, with 90% confidence interval (CI; 1.09-1.38). In healthy female subjects receiving ethinyl estradiol/ levonorgestrel oral contraceptives, repeat daily crinecerfont had no effect on ethinyl estradiol or levonorgestrel AUC (INT11387). Thus, crinecerfont was considered in humans in vivo as a weak inhibitor of CYP3A4. CYP3A4 inhibitors do not have a significant impact on crinecerfont exposure. Crinecerfont is neither a P-glycoprotein (P-gp) substrate, nor a P-gp inhibitor.

Overall, crinecerfont was well tolerated as a single dose of up to 800 mg or a repeated dose of up to 400 mg/day for 16 days in a total of 363 subjects in Phase 1 studies. No apparent dose-relationship was observed in the incidence of treatment-emergent adverse events (TEAEs). The nature and frequency of TEAEs were comparable among the different dose groups and formulations. Overall, 3 serious adverse events (SAEs) were reported in 2 subjects (colitis in one subject and back pain and hematochezia in another subject) at the highest single dose of 800 mg with the free base lipidic formulation. No clinically relevant changes were observed in safety laboratory parameters including hormone levels (ACTH, cortisol, testosterone, thyroid stimulating hormone, free triiodothyronine, free thyroxine, prolactin, growth hormone, luteinizing hormone, and follicle-stimulating hormone), vital signs, and electrocardiogram (ECG) parameters.

Crinecerfont was also well tolerated up to a repeated dose of 100 mg/day for 56 days in the Phase 2 study in 361 male and female subjects with MDD (DFI5687). The most frequently reported TEAEs (more than 5% in any crinecerfont group and higher than placebo) were headache, nausea, dry mouth, dizziness, somnolence, constipation, fatigue, and neutropenia. One death (completed suicide) occurred in the study (crinecerfont 100 mg group); this event occurred approximately 3 weeks after the subject's last dose of study drug. The percentage of subjects with suicidal ideation or behavior during treatment was similar between the 5 treatment groups. The percentages of treatment-emergent SAEs were similar among the 3 crinecerfont treatment groups (0.8% in each crinecerfont group) and the placebo group (1.7%), but slightly higher in the escitalopram 10 mg group (4.3%). Overall, approximately 10% of subjects discontinued due to TEAEs, most commonly neutropenia. The subjects receiving crinecerfont with the TEAE of neutropenia were asymptomatic, and these values recovered/resolved within 20 days of occurrence. Analyses of potentially clinically significant abnormalities for laboratory, vital signs, and ECG showed similar results between the 5 treatment groups.

5.3. Study and Dose Rationale

The present Phase 3 randomized, double-blind, placebo-controlled study is designed to evaluate the efficacy, safety, and tolerability of crinecerfont regimen of 100 mg administered twice daily (bid) in adult subjects with classic CAH due to 21-hydroxylase deficiency. Repeated total daily doses in the range of 100 mg to 300 mg, including bid dosing, have been well tolerated in Phase 1 and Phase 2 studies. Exposure-response analysis using data from the administration of crinecerfont prior to a corticotropin releasing factor-challenge test in healthy subjects and simulations of crinecerfont plasma concentrations following various dose regimens suggest that a

crinecerfont dose of 100 mg bid will result in sustained CRF_1 receptor antagonist activity over the entire day. These data are supported by the results of Study NBI-74788-CAH2001, where subjects with classic CAH received crinecerfont 50 mg at bedtime, 100 mg at bedtime, 100 mg every evening (qPM), or 100 mg bid. This study demonstrated that administration of 100 mg bid crinecerfont led to meaningful median reductions in ACTH and 17-OHP (54% to 75% from baseline) as well as androstenedione concentrations in subjects with classic CAH after 14 days of treatment. A dose-response for androstenedione was observed with approximately 20% median reduction from baseline with the 50 mg dose, approximately 40% with each of the 100 mg once daily doses, and approximately 60% with the 100 mg twice daily dose. Crinecerfont was well tolerated at all dose regimens evaluated. Adverse events were mostly mild, with 1 SAE of cholelithiasis that occurred 34 days after the last dose of study drug and was assessed as unrelated to study drug reported in a subject receiving 100 mg at bedtime. Adverse events reported in 2 or more subjects included headache, upper respiratory tract infection, fatigue, contusion, insomnia, nausea, and viral upper respiratory tract infection. There were no safety concerns related to laboratory, vital signs, or ECG results.

Based on the corticotropin releasing factor-challenge test in healthy subjects as well as the Phase 2 data in subjects with classic CAH, a dose of 100 mg bid was selected for evaluation in this Phase 3 study. At Month 12, subjects who did not respond adequately to the 100 mg bid dose will be randomly assigned to receive a higher evening dose of 200 mg to target the overnight ACTH surge while retaining the 100 mg dose in the morning to provide CRF_1 receptor antagonist activity during the day. The crinecerfont 100 mg qAM/200 mg qPM dose regimen is supported by results from a 28-day placebo-controlled study (Study NBI-74788-1724) evaluating safety, tolerability, and PK of two dosing regimens of crinecerfont (100 mg qAM/150 mg qPM or 100 mg qAM/200 mg qPM) in healthy male and female subjects. The study demonstrated that a regimen of 100 mg qAM and 200 mg qPM was well tolerated with adequate safety margins to support chronic dosing. Adverse events were all mild or moderate, no SAEs were reported, and no safety concerns related to routine laboratory tests, vital signs, or ECGs were observed. One non-serious TEAE of hypersensitivity (moderate in intensity; assessed as possibly related to study drug by the investigator) occurred with the crinecerfont 100 mg qAM/150 mg qPM regimen and led to discontinuation of study drug. The event resolved following treatment with oral corticosteroids and antihistamines.

At Month 24, investigators will have the option of dosing subjects with adequate disease control with crinecerfont once daily as 200 mg qPM. Adrenal hypertrophy has been reported to be associated with excess adrenal androgen production (El-Maouche et al., 2019). Further, Jha et al., 2019 have reported decreased adrenal tissue (TART) size following suppression of ACTH with moderate doses of dexamethasone for 5 months. At Month 24, all subjects in this study will have been treated with crinecerfont for 18 to 24 months, which is sufficient time for a potential decrease in adrenal size to occur. As decreased adrenal size may result in easier control of androgens, well-controlled subjects may be adequately treated with a single daily dose of crinecerfont (administered as 200 mg qPM to suppress the morning ACTH surge), thus reducing their treatment burden.

6. STUDY OBJECTIVES

The objectives of this study are:

- To evaluate the efficacy of crinecerfont (100 mg bid), compared with placebo, in reducing daily glucocorticoid dosage while maintaining adrenal androgen control.
- To evaluate the efficacy of crinecerfont, compared with placebo, in reducing adrenal steroid levels following an initial 4-week treatment period.
- To evaluate the effect of crinecerfont, compared with placebo, on clinical endpoints associated with supraphysiologic glucocorticoid dosing.
- To evaluate plasma concentrations of crinecerfont and metabolites.
- To assess the safety and tolerability of crinecerfont.
- To evaluate an alternate dosing regimen of crinecerfont in subjects who have not reduced their glucocorticoid dose by Month 12.

7. STUDY DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of crinecerfont versus placebo administered bid with breakfast and the evening meal (doses separated by approximately 12 hours) for 24 weeks in approximately 165 adult subjects with classic CAH due to 21 hydroxylase deficiency. Eligible subjects will be randomly assigned in a 2:1 ratio (active:placebo) to 2 treatment groups, crinecerfont 100 mg bid or placebo. After the 24-week randomized treatment period, there will be a 6 month, open-label treatment period, during which all subjects will receive crinecerfont 100 mg bid. At Month 12, subjects who have not reduced their glucocorticoid dose to ≤11 mg/m^2/day will be re-randomized (2:1) to receive 100 mg qAM and 200 mg qPM or to continue 100 mg bid, in a blinded fashion. Subjects who have reduced their glucocorticoid dose to ≤11 mg/m^2/day will continue to receive 100 mg bid in an open-label fashion. At Month 18, subjects will review applicable portions of the informed consent form and confirm whether they will participate in the optional OLE treatment period for continued access to crinecerfont.

During the OLE, subjects will have their glucocorticoid doses adjusted as appropriate and tolerated to achieve the lowest glucocorticoid dose that maintains adequate disease control (in the opinion of the investigator). The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents.

Starting at Month 18, all subjects who are continuing in the OLE will initially receive crinecerfont 100 mg bid. If the subject has inadequate disease control despite receiving glucocorticoid treatment at their target dose (in the opinion of the investigator), the crinecerfont dose may be increased to 100 mg qAM and 200 mg qPM. After the Month 24 visit, an alternative dosing regimen of once daily 200 mg qPM can be considered per the investigator (see Appendix C, Open-Label Extension Treatment Period Glucocorticoid and Crinecerfont Dose Adjustment Guidance).

Subjects will remain in the OLE until crinecerfont becomes commercially available, the Sponsor elects to discontinue development of crinecerfont for CAH, the Sponsor elects to discontinue the

study, or the subject meets one of the study withdrawal criteria. A final study visit will be conducted approximately 4 weeks after the last dose of study drug.

An independent Data Monitoring Committee (DMC) will periodically review ongoing clinical safety data to ensure the safety and well-being of study subjects. An interim analysis is planned after approximately 83 subjects (50% of planned sample size) have had the opportunity to complete the Week 24 assessments. At this time the primary endpoint will be evaluated for futility and unblinded sample size re-estimation based on the estimated treatment effect and the conditional power. The interim analysis will be performed using the "promising zone" approach (Mehta and Pocock, 2011). The DMC will recommend one of the following actions: stop the study for futility, increase the sample size up to a maximum of 210 subjects, or continue the study as planned, with no increase in sample size. Further details are contained in Section 13.7.

Screening Period (Weeks -4 up to Day -1)

All subjects must provide signed and witnessed informed consent (which may be done remotely, if allowed and remote consenting procedures are in place) prior to the conduct of any study-related procedures. Subjects will undergo screening for up to 4 weeks (Weeks -4 to Day -1) to determine eligibility, with assessments performed according to the Schedule of Assessments (Table 1). There will be a second visit (at home or the study site) during the screening period to collect a blood sample (for hormone measurements). The screening period may be extended by 2 weeks (if needed) for results of Screening Visit 2 hormone tests. Subjects must be on a supraphysiologic glucocorticoid regimen defined as >13 mg/m^2/day in hydrocortisone dose equivalents (Appendix A) adjusted for body surface area (BSA) that has been stable at least 1 month leading up to screening. The glucocorticoid regimen should be optimized by the treating physician to achieve control of adrenal androgen levels and minimization of glucocorticoid dosage to the extent appropriate for the subject's individual medical needs and treatment goals.

Rescreening is permitted if a subject does not meet all eligibility requirements and returns to be rescreened. A subject that has failed screening twice may not be rescreened again without prior permission from the Medical Monitor.

Randomized, Double-Blind, Placebo-Controlled Treatment Period (Day 1 up to Week 24)

4-Week Glucocorticoid Stable Period (Day 1 up to Week 4)

During the first 4 weeks of the study, subjects should maintain their stable glucocorticoid regimen, except for sick-day guidelines. Sick-day dosing may follow guidelines outlined in Appendix B or will be based on guidance provided by the investigator or their treating physician.

On Day 1 (baseline), subjects will collect a urine sample (all voids from midnight the night before the study visit to the first morning void after awakening for the day) at home in the morning and bring it to the site for measurement of androgen metabolite levels. They will hold their morning glucocorticoid dose and bring it with them to the study site so that a blood sample can be obtained prior to taking the morning glucocorticoid dose; subjects will then take their morning dose of glucocorticoid at the study site, and another blood sample will be taken approximately 2 hours postdose in order to establish the baseline pre- and post-glucocorticoid hormone levels. Subjects should be fasting from the night before so that fasting blood tests and an oral glucose tolerance test can be performed, but should be encouraged to drink water to avoid any hypovolemic status.

Subjects will be randomized on Day 1 in a 2:1 ratio (active:placebo). Randomization will be stratified by total daily glucocorticoid dose, glucocorticoid type, and sex. Beginning on Day 1 (baseline), study drug will be administered at home with the subject's evening meal; thereafter, study drug will be administered bid with the subject's breakfast and evening meal (doses separated by approximately 12 hours).

8-Week Glucocorticoid Reduction Period (Week 4 up to Week 12)

During this period, subjects will undergo a down-titration (in 4 or fewer steps) of their glucocorticoid dose with the goal to reach a target dose of 8 to 10 mg/m^2/day (hydrocortisone equivalents adjusted for BSA) by Week 12, unless the subject has any signs or symptoms suggestive of clinically relevant glucocorticoid insufficiency or unacceptable symptoms of hyperandrogenism (see below and Section 9.3.1 for additional details on the glucocorticoid dose reduction schedule).

At the Week 4 visit, a similar procedure will be followed as for Day 1 to obtain a more detailed assessment of androgen status, with collection of a urine sample at home and collection of blood samples prior to and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. At this visit, the investigator will instruct the subject on the first step of the glucocorticoid dose reduction and arrange to contact the subject by telephone within a week of the study visit to assess how the subject is tolerating the glucocorticoid dose reduction. During the follow-up telephone contact, if the investigator feels that a clinical assessment and/or laboratory tests are needed, these can be performed as an unscheduled visit.

Subjects will have study visits at Weeks 6 (at home or the study site), 9 (at home or the study site), and 12 for study assessments, including collection of blood samples to assess hormone levels and routine safety assessments.

At the Week 6 visit, the investigator will instruct the subject on the second step of the glucocorticoid dose reduction (if applicable) and, if a glucocorticoid dose reduction occurred, will arrange to contact the subject by telephone within a week of the study visit to assess how the subject is tolerating the glucocorticoid dose reduction. The investigator will contact the subject at approximately Week 8 to advise on the third step of glucocorticoid dose reduction (if applicable).

At the Week 9 study visit, the investigator will assess whether the subject is tolerating the third glucocorticoid dose reduction (if applicable). The investigator will contact the subject at approximately Week 10 to advise on the fourth step of glucocorticoid dose reduction (if applicable) and, if a glucocorticoid dose reduction occurred, will arrange to contact the subject by telephone within a week of the study visit to assess how the subject is tolerating the glucocorticoid dose reduction.

If the subject experiences any of the following signs or symptoms at any time during the glucocorticoid dose reduction process, the glucocorticoid dose should NOT be reduced further but returned to the previous dose that was tolerated. However, before the glucocorticoid dose reduction is stopped for symptoms or signs of orthostatic hypotension, volume status should be optimized (eg, with additional dietary salt, salt tablets, intravenous saline).

- Unexplained hyponatremia (serum sodium <135 mmol/L)
- Orthostatic hypotension with decrease in systolic blood pressure >20 mmHg or in diastolic blood pressure >10 mmHg after standing (from a seated position) after approximately 2 minutes, or severe symptoms of dizziness or lightheadedness upon standing
- Severe nausea, food aversion, vomiting
- Unacceptable symptoms of hyperandrogenism (eg, hirsutism, acne, amenorrhea)

Glucocorticoid dose reductions during Weeks 4 to 12 should proceed even if androstenedione levels increase transiently, provided that the increase is asymptomatic and tolerated by the subject.

At the Week 12 visit, based on review of the subject's hormone levels collected up to that visit as well as based on clinical assessment, the investigator will determine the appropriate dose of glucocorticoid to continue past Week 12 (the reduced dose if tolerated, or a prior [higher] dose) in order to achieve adequate control of androgen levels (ie, androstenedione ≤120% of the subject's baseline or ≤upper limit of normal [ULN] for age and sex).

12-Week Glucocorticoid Optimization Period (Week 12 up to Week 24)

Subjects will continue on the glucocorticoid regimen as instructed by the investigator at Week 12 and return to the study site at Week 16 (at home or the study site), Week 20 (at home or the study site), and Week 24 during the glucocorticoid optimization period. At these visits, the investigator will review the laboratory results from the preceding study visit and determine if the glucocorticoid regimen requires adjustment in order to achieve adequate control of androgen levels (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex).

At the Week 24 visit, subjects will follow a similar procedure as Day 1 for additional androgen assessments with collection of a urine sample at home and collection of blood samples prior to and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. Subjects should be fasting from the night before, but should be encouraged to drink water to avoid any hypovolemic status, and a glucose tolerance test will be performed (with study drug taken with the glucose load rather than a meal).

Open-Label Treatment Period (Week 24 up to Month 12)

For the purpose of this study, months are defined as 4-week intervals.

Starting the evening of the Week 24 visit (after all Week 24 assessments have been performed), all subjects will receive active study drug (crinecerfont) 100 mg bid with breakfast and evening meals. Subjects should continue the glucocorticoid regimen specified by the investigator at

Week 24. Subjects and investigators will remain blinded to subjects' treatment group assignment from the double-blind period.

1-Month Glucocorticoid Stable Period (Week 24 up to Month 7)

During the first month of open-label treatment with crinecerfont, subjects should maintain a stable glucocorticoid regimen (except for sick-day guidelines; Appendix B).

3-Month Glucocorticoid Reduction Period (Month 7 up to Month 10)

At Months 7 (at home or the study site), 8, and 9 (at home or the study site), investigators will decrease glucocorticoid doses in those subjects whose glucocorticoid dose is still greater than 11 mg/m^2/day at Month 7 (unless there is a safety concern with regard to glucocorticoid insufficiency), with the goal to achieve a target physiologic dose of 8 to 10 mg/m^2/day by Month 10. The glucocorticoid dose should be reduced by approximately 10% to 20% at each visit (Months 7, 8, and 9), as long as androstenedione levels are controlled (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex) and the subject is not experiencing any signs or symptoms suggestive of clinically relevant glucocorticoid insufficiency or unacceptable symptoms of hyperandrogenism (Section 9.3.1). The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents. After each of the glucocorticoid dose reduction steps, the site should contact the subject by telephone (within a week) to assess how the subject is tolerating the glucocorticoid dose reduction. Subjects will have study visits at Months 8, 9, and 10 for study assessments including collection of blood samples for hormone levels.

2-Month Glucocorticoid Maintenance Period (Month 10 up to Month 12)

Subjects will have study assessments at Month 10 (at home or the study site) and Month 12 as outlined in the Schedule of Assessments. During this period, the goal should be to maintain stable glucocorticoid doses; however, the dose can be adjusted according to standard of care (eg, to achieve the control of androgen levels appropriate to the treatment targets for each subject).

At the Month 12 visit, subjects will have additional androgen assessments with collection of a urine sample at home and blood sample collection before and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. Subjects should be fasting from the night before (subjects should be encouraged to drink water to avoid any hypovolemic status). A glucose tolerance test will be performed (with study drug taken with the glucose load rather than a meal) at the Month 12 visit.

Open-Label or Double-Blind Active-Controlled Treatment Period (Month 12 to Month 18)

6-Month Glucocorticoid Maintenance Period (Month 12 to Month 18) for Subjects with Month 12 Glucocorticoid Dose ≤11 mg/m^2/day

Subjects with glucocorticoid dose ≤11 mg/m^2/day at Month 12 will continue on active study drug at 100 mg bid until Month 18 with study visits at Months 14 (at home or the study site), 16 (at home or the study site), and 18. The goal during this period is to maintain stable glucocorticoid doses while androstenedione levels are controlled (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex), although the dose can be adjusted according to standard of care.

At the Month 18 visit, subjects will have additional androgen assessments with collection of a urine sample at home and blood sample collection before and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. Subjects should be fasting from the night before (subjects should be encouraged to drink water to avoid any hypovolemic status).

6-Month Glucocorticoid Reduction/Optimization (Month 12 to Month 18) for Subjects with Month 12 Glucocorticoid Dose >11 mg/m^2/day

Subjects with glucocorticoid dose >11 mg/m^2/day at Month 12 will be re-randomized (2:1) to adjust active study drug dose to 100 mg qAM and 200 mg qPM or to continue active study drug at 100 mg bid; study drug will be blinded such that all re-randomized subjects will be taking the same number of capsules. Subjects should maintain a stable glucocorticoid regimen (except for sick-day guidelines [Appendix B]) for the first month until the Month 13 visit. At the Month 13 visit, subjects will have additional androgen assessments with collection of a urine sample at home and blood sample collection before and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site.

At Months 13, 14 (at home or the study site), and 16 (at home or the study site), investigators will decrease glucocorticoid doses with the goal to achieve a target physiologic dose of 8 to 10 mg/m^2/day by Month 18. The glucocorticoid dose should be reduced by approximately 10% to 20% at Months 13, 14, and 16, as long as androstenedione levels are controlled (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex) and the subject is not experiencing any signs or symptoms suggestive of clinically relevant glucocorticoid insufficiency or unacceptable symptoms of hyperandrogenism. The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents. After each of the glucocorticoid dose reduction steps, the site should contact the subject by telephone (within a week) to assess how the subject is tolerating the glucocorticoid dose reduction.

At the Month 18 visit, subjects will have additional androgen assessments with collection of a urine sample at home and blood sample collection before and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. Subjects should be fasting from the night before (subjects should be encouraged to drink water to avoid any hypovolemic status).

Open-Label Extension (OLE) Treatment Period for Continued Crinecerfont Access (Month 18 Onwards)

At Month 18, subjects will review applicable portions of the informed consent form and confirm whether they will participate in the optional OLE. During the OLE, subjects will have their glucocorticoid doses adjusted as appropriate and tolerated to achieve the lowest glucocorticoid dose that maintains adequate disease control (in the opinion of the investigator). The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents. After each glucocorticoid dose reduction, the site should contact the subject by telephone (within a week) to assess how the subject is tolerating the glucocorticoid dose reduction.

Starting at Month 18, all subjects who are continuing in the OLE will initially receive open-label crinecerfont 100 mg bid. If the subject has inadequate disease control despite receiving glucocorticoid treatment at their target dose (in the opinion of the investigator), the crinecerfont dose may be increased to 100 mg qAM and 200 mg qPM (including at Month 18, after laboratory results are available). If the increased dose of 100 mg qAM and 200 mg qPM is not

well tolerated, the dose may be reduced back to 100 mg bid. After the Month 24 visit, an alternative dosing regimen of once daily 200 mg qPM can be considered per the investigator (Appendix C). Crinecerfont doses should generally only be adjusted at or shortly after study visits (after laboratory results are available).

In the setting of inadequate disease control, if the glucocorticoid dose is at or above the target, an increase in the glucocorticoid dose should generally be considered only after the crinecerfont dose has been maximized for the subject. Changes to the glucocorticoid and crinecerfont doses should generally be separated by at least 1 month in order to assess the effect of each change.

Study visits during the OLE will occur every 3 months until Month 24, and every 6 months thereafter, with the option of having the Month 21 visit at home.

At the Month 24 visit, and every 12 months thereafter, subjects will have blood sample collection before and approximately 2 hours after dosing of morning glucocorticoid and study drug at the study site. Subjects should be fasting from the night before (subjects should be encouraged to drink water to avoid any hypovolemic status). A glucose tolerance test will also be performed at Month 24 and every 12 months thereafter (with study drug taken with the glucose load rather than a meal).

Subjects will remain in the OLE until crinecerfont becomes commercially available, the Sponsor elects to discontinue development of crinecerfont for CAH, the Sponsor elects to discontinue the study, or the subject meets one of the study withdrawal criteria.

Follow-Up Period

A final posttreatment visit will be conducted approximately 1 month after subjects' final dose of study drug. This visit is not required if the subject transitions during the OLE to taking commercially-available crinecerfont or to another crinecerfont study.

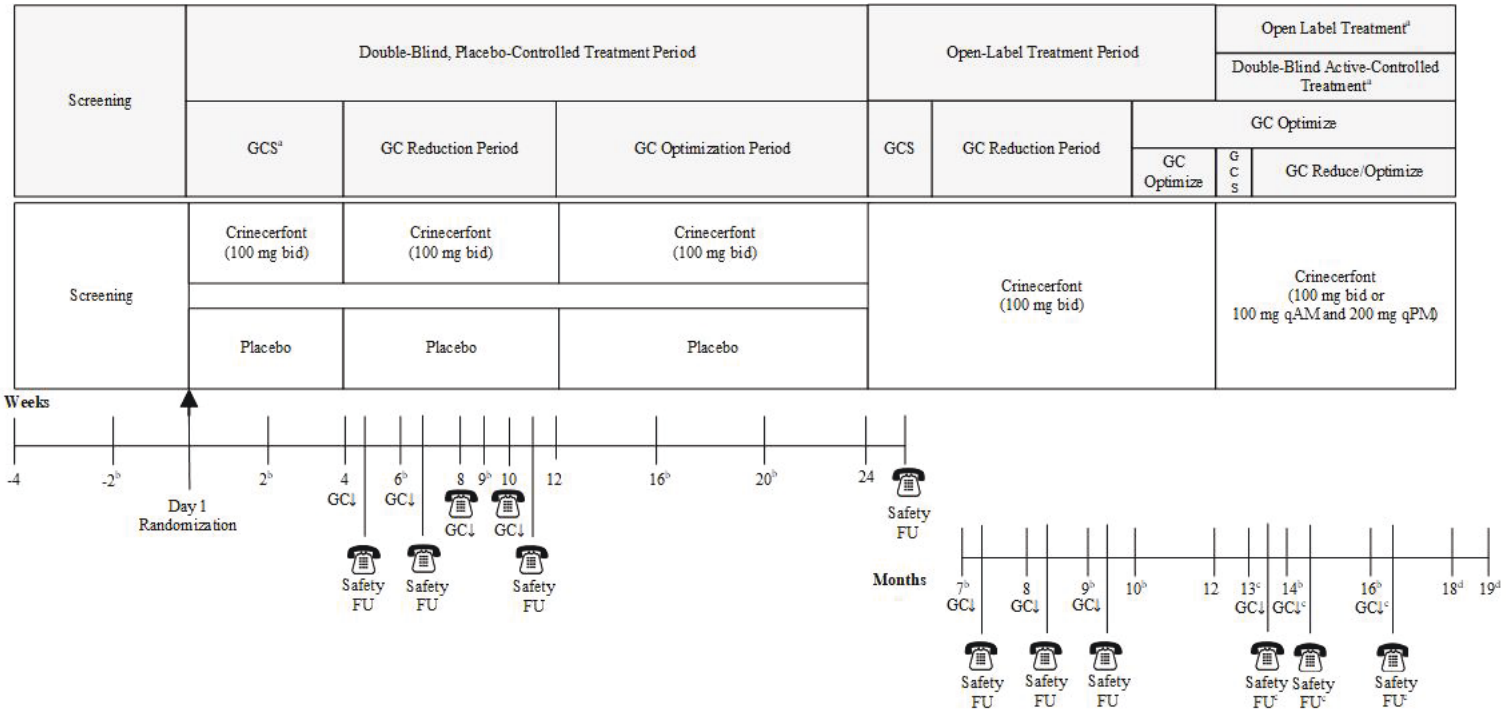
Study Assessments and Study Visit Scheduling

Efficacy, safety, and PK will be assessed at scheduled times throughout the study. As much as possible, all study visits (including baseline and follow-up) should occur at approximately the same time in the morning to standardize time of day for assessment of efficacy, safety, and drug exposure.

In the double-blind, placebo-controlled portion of the study, all visits after Day 1 during the glucocorticoid stable period and glucocorticoid reduction period have a visit window of +5 days, and all visits during the glucocorticoid optimization period have a visit window of ±5 days. In the open-label or double-blind active-controlled treatment period, visits from Month 7 to Month 10 have a visit window of ±5 days and visits from Month 12 to Month 18 will have a visit window of ±7 days. During the OLE, visits will have a visit window of ±14 days. If a subject's glucocorticoid regimen is adjusted due to sick-day guidelines, the subject should resume their glucocorticoid dosing regimen for at least 3 days before their next scheduled hormone panel assessment, and this 3-day window supersedes all other visit windows.

A schematic of the study design is shown in Figure 1.

Figure 1: Study Design Schematic for Double-Blind Placebo-Controlled Treatment Period, Open-Label Treatment Period and Double-Blind Active-Controlled Treatment Period



bid=twice daily; FU=follow-up; GC=glucocorticoid; GCS=Glucocorticoid Stable Period.

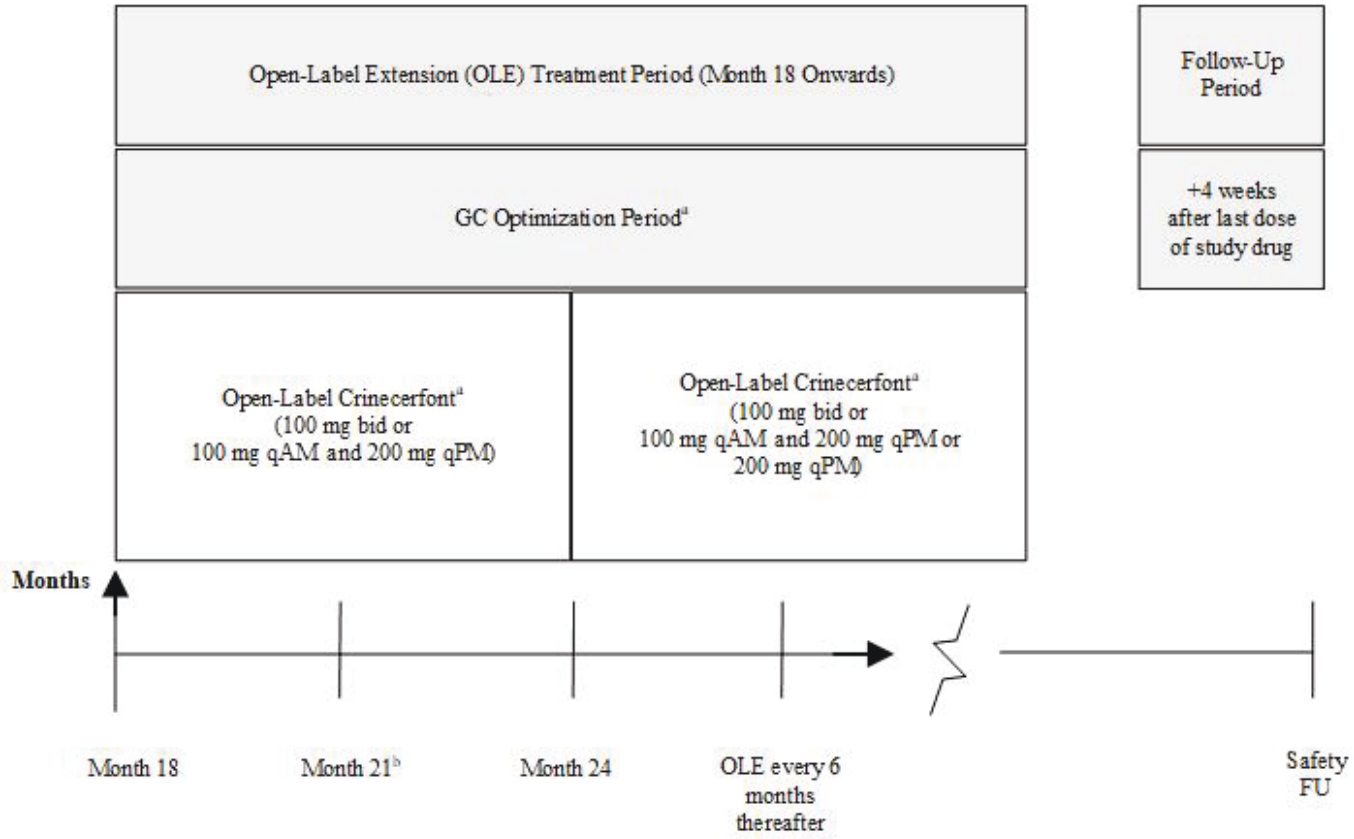
[a] Subjects with GC dose ≤11 mg/m^2/day at Month 12 will continue to receive open-label treatment. Subjects with GC dose >11 mg/m^2/day at Month 12 will be re-randomized to 1 of 2 active treatment regimens (continue 100 mg bid or 100 mg qAM, 200 mg qPM).

[b] At home or study site.

[c] Only for re-randomized subjects.

[d] Subjects who do not enter the OLE will undergo a follow-up visit approximately 28 days after the last dose of study drug.

Figure 2: Study Design Schematic for Optional Open-Label Extension (OLE) Treatment Period for Continued Access (Month 18 Onwards)



bid=twice daily; FU=follow-up; GC=glucocorticoid; OLE=open-label extension

[a] At Month 18, subjects will review applicable portions of the informed consent form and confirm whether they will participate in the optional OLE. All subjects in the OLE will initially receive open-label crinecerfont 100 mg bid. If the subject has inadequate disease control despite receiving glucocorticoid treatment at their target dose (in the opinion of the investigator), the crinecerfont dose may be increased to 100 mg qAM and 200 mg qPM (including at Month 18, after laboratory results are available). If the increased dose of 100 mg qAM and 200 mg qPM is not well tolerated, the dose may be reduced back to 100 mg bid (Appendix C). After the Month 24 visit, an alternative dosing regimen of once daily 200 mg qPM can be considered per the investigator. During the OLE, subjects will have their GC doses adjusted as appropriate and tolerated to achieve the lowest GC dose that maintains adequate disease control (in the opinion of the investigator). After each GC dose reduction, the site should contact the subject by telephone (within a week) to assess how the subject is tolerating the GC dose reduction.

[b] The Month 21 visit may be performed at home or at the study site.

8. STUDY POPULATION

This study will be conducted in approximately 165 female and male subjects, at least 18 years of age, with a documented medical diagnosis of classic CAH due to 21-hydroxylase deficiency. Subjects must meet all inclusion criteria and no exclusion criteria to participate.

8.1. Subject Inclusion Criteria

To participate in this study, subjects must meet the following criteria:

1. Subjects must provide written informed consent.
2. Be a female or male at least 18 years of age.
3. Have a medically confirmed diagnosis of classic 21-hydroxylase deficiency CAH based on standard medically accepted criteria such as elevated 17-OHP level, confirmed CYP21A2 genotype, positive newborn screening with confirmatory second-tier testing, or cosyntropin stimulation.
4. Be on a stable, supraphysiologic glucocorticoid dose regimen (defined as >13 mg/m^2/day in hydrocortisone dose equivalents) that has been stable for at least 1 month prior to screening, is intended for chronic use, and consists of 1 or more of the following orally administered glucocorticoids: hydrocortisone, prednisone, prednisolone, methylprednisolone, or dexamethasone (Appendix A).
5. If treated with fludrocortisone, dose should be stable for at least 1 month prior to screening with an upright plasma renin activity (PRA) during screening that is not greater than ULN on the subject's usual sodium intake. If PRA is >ULN, the subject must have systolic blood pressure >100 mmHg, without orthostatic hypotension, and with serum sodium and potassium in the normal range.
6. Female subjects of childbearing potential with fertile male partners must agree to use contraception consistently from screening until the final study visit or 30 days after the last dose of study drug, whichever is longer. A subject who is not of childbearing potential must meet one of the following:

    - Postmenopausal, defined as no menses for 12 months without an alternative medical cause and confirmed by elevated follicle-stimulating hormone (FSH) consistent with a postmenopausal range.
    - Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy

    Acceptable methods of contraception are listed in Section 9.9.1.

8.2. Subject Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Have a known or suspected diagnosis of any of the other forms of classic CAH including 11-β-hydroxylase deficiency, 17-α-hydroxylase deficiency, 3-β-hydroxysteroid dehydrogenase deficiency, P450 side-chain cleavage deficiency, or P450 oxidoreductase deficiency.
2. Have a history of bilateral adrenalectomy, hypopituitarism, or other condition requiring chronic therapy with oral glucocorticoids, or requiring chronic therapy with inhaled glucocorticoids that based on dose and hormone profile the investigator deems would yield significant systemic exposure interfering with study endpoints.
3. Evidence of glucocorticoid overtreatment during screening, as evidenced by pre-glucocorticoid morning 17-OHP less than the ULN, post-glucocorticoid morning 17-OHP less than the lower limit of normal, or morning androstenedione level less than the lower limit of normal, based on normal ranges for age and sex.
4. At increased risk of developing adrenal crisis in the Investigator's opinion, based on, for example, repeated history of adrenal crisis in the past, prior history of adrenal crisis precipitated by reducing glucocorticoid dose, recent episode(s), etc.
5. Have a clinically significant medical condition or chronic disease (including history of neurological, hepatic, renal, cardiovascular, gastrointestinal, significant malabsorption, hematologic, pulmonary, psychiatric, or endocrine disease [excluding CAH]) that in the opinion of the investigator would preclude the subject from participating in and completing the study or that could confound interpretation of study outcome.
6. History of malignancy, unless successfully treated with curative intent and considered to be cured.
7. Have a known history of clinically concerning cardiac arrhythmia (including long QT syndrome) or prolongation of screening (pre-treatment) QT interval corrected for heart rate using Fridericia's correction (QTcF) of >450 msec (males) or >470 msec (females).
8. Known sensitivity (ie, hypersensitivity) or allergy to any corticotropin-releasing hormone (CRH) receptor antagonist.
9. Have evidence of chronic renal or liver disease based on any of these screening laboratory test abnormalities:
    - Serum creatinine >1.5 × ULN.
    - Aspartate aminotransferase (AST) >3 × ULN.
    - Alanine aminotransferase (ALT) >3 × ULN.
    - Total bilirubin >1.5 × ULN unless due to a documented diagnosis of Gilbert's syndrome.
10. Have any of the following hematologic abnormalities at screening:
    - Hemoglobin <10 g/dL.
    - White blood cell (WBC) count $<3.0 \times 10^3/mm^3$.
    - Platelet count $<100,000/mm^3$.

- Absolute neutrophil count $<1.0 \times 10^3/mm^3$.

11. Have any of the following coagulation abnormalities at screening:
    - Activated partial thromboplastin time (aPTT) that exceeds ULN values by more than 5 seconds.
    - Prothrombin time (PT) expressed as international normalized ratio (INR) >1.3, unless the subject is on anticoagulant treatment that affects INR.
12. Used any active investigational drug in the context of a clinical trial within 30 days or 5 half-lives (whichever is longer) before screening, or plans to use such an investigational drug (other than the study drug) during the study.
13. Are using any excluded concomitant medication and cannot discontinue use of these medications for the duration of the study (also refer to Section 9.9.1):
    - Orally administered glucocorticoids for indications other than CAH.
    - Strong inducers of CYP3A4 or CYP2B6 except topically administered medications.
    - Medications that affect cortisol or glucocorticoid metabolism (eg, phenytoin, mitotane, phenobarbital, strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, cholestyramine, certain antivirals) except topically administered medications.
    - Aromatase inhibitors (eg, anastrozole, letrozole, testolactone).
14. Has current substance dependence or substance or alcohol abuse (drugs including controlled substance or non-prescribed use of prescription drugs; nicotine and caffeine dependence are not exclusionary).
15. Have a significant risk of suicidal or violent behavior. Subjects with any suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) in the past 6 months before screening or any history of suicidal behavior within the past year based on the Columbia-Suicide Severity Rating Scale (C-SSRS) should be excluded.
16. Have had a blood loss ≥550 mL or donated blood or blood products within 8 weeks before Day 1 (baseline).
17. Females who are pregnant or lactating.
18. In the Investigator's opinion, the subject is not capable of adhering to the protocol requirements.

8.3. Subject Identification and Replacement of Subjects

Subjects will be identified by their unique subject number. The subject number will be noted on electronic case report forms (eCRFs), all source documentation, laboratory documents, and ECG tracings. Subjects who discontinue from the study will not be replaced.

8.4. Randomization

Eligible subjects will be randomized 2:1 to either crinecerfont or placebo on Day 1 using an interactive response technology (IRT). Randomization will be stratified by total daily glucocorticoid regimen on Day 1 (<20 mg/m^2/day or ≥20 mg/m^2/day in hydrocortisone dose equivalents adjusted for BSA; see Appendix A), glucocorticoid type (hydrocortisone alone; prednisone, prednisolone, methylprednisolone, with or without hydrocortisone; dexamethasone, with or without another glucocorticoid), and sex.

Subjects with glucocorticoid dose >11 mg/m^2/day (hydrocortisone dose equivalents) at Month 12 will be re-randomized 2:1 to a modified regimen of 100 mg qAM and 200 mg qPM or to continue crinecerfont at 100 mg bid. Month 12 randomization will be stratified by the original treatment assignment (crinecerfont versus placebo) and by Month 12 glucocorticoid dose (>14 mg/m^2/day versus ≤14 mg/m^2/day). Subjects who discontinue study drug prior to Month 12 are ineligible for re-randomization.

9. STUDY EVALUATIONS

9.1. Schedule of Assessments

A schedule of assessments for the screening and double-blind, placebo-controlled treatment period and the open-label and double-blind active-controlled treatment periods is shown in Table 1 and Table 2, respectively. Subjects will provide written informed consent (which may be done remotely, if allowed and remote consenting procedures are in place) before any study-related procedures are performed. At Month 18, subjects will review applicable portions of the informed consent form and confirm whether they will participate in the optional OLE for continued access to crinecerfont (Table 3). Subject-related events and activities including specific instructions, procedures, concomitant medications, dispensing of study drug, and descriptions of AEs should be recorded in the appropriate source documents and eCRFs.

Table 1: Schedule of Assessments – Screening and Double-Blind, Placebo-Controlled Treatment Period

Assessment	Screening (Week -4 to Day -1)[a]		Double-Blind, Placebo-Controlled Treatment Period										
			GC Stable Period[a]		GC Reduction Period[a]						GC Optimization Period[a]		
	Visit 1	Visit 2[b]	Day 1 (Baseline)	Week 2[b]	Week 4[c]	Week 6[b,c]	Week 8	Week 9[b]	Week 10[c]	Week 12	Week 16[b]	Week 20[b]	Week 24
Informed consent	X		X[d]		X[d]								
I/E criteria	X		Update										
Medical history	X		Update										
UDS	X												
Physical exam[e]	X		X		X					X			X
Orthostatics[f]	X		X			X		X		X			X
Vital signs and weight[g]	X		X		X	X		X		X	X	X	X
Chemistry labs	X		X		X	X		X		X	X	X	X
Hematology/coagulation	X		X		X					X			X
Urinalysis	X		X		X					X			X
PK blood sample			X	X	X	X		X		X	X	X	X
CYP21A2 genotyping			X										
Pregnancy test[h]	X (s)		X (u)		X (u)			X (u)		X (u)	X (u)	X (u)	X (u)
Hormone panel[i]	X	X	X	X	X	X		X		X	X	X	X
TSH and free T4	X (TSH only)		X		X								X
Urine androgen[j]			X		X								X
Fasting metabolic panel[k]			X										X
Bone markers[l]			X										X
Glucose tolerance test[m]			X										X
Testicular U/S[n]			X										X
DXA			X										X
SF-36			X										X
EQ-5D-5L			X										X
MAF			X										X
MOS-12			X										X
PGWBI			X										X
BPRS	X		X							X			X
C-SSRS	X		X		X			X		X	X	X	X
Hirsutism and Acne Scale[o]			X		X					X			X
Menstrual Questionnaire[o]	X		X		X			X		X	X	X	X
12-lead ECG	X		X		X								X
Potential GC reduction					X	X	X		X				
Onsite dosing[p]			X		X								X
Dispense study drug			X		X					X			X
Study drug accountability[q]					X					X			X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior & concomitant medications	X		X		X	X		X		X	X	X	X

AE=adverse event; BPRS=Brief Psychiatric Rating Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP=cytochrome P450; DXA=dual-energy X-ray absorptiometry; ECG=electrocardiogram; ET=early termination; GC=glucocorticoid; HbA1c=glycated hemoglobin; I/E=inclusion/exclusion; MAF=Multidimensional Assessment of Fatigue; MOS-12=Medical Outcomes Study 12-item Sleep Scale; PGWBI=Psychological General Well-Being Index; PK=pharmacokinetics; PRA=plasma renin activity; s=serum; SF-36=36-Item Short Form Health Survey; U/S=ultrasound; T4=thyroxine; TSH=thyroid stimulating hormone; u=urine; UDS=urine drug screen.

[a] Screening period may be extended by 2 weeks (if needed) for the results of Screening Visit 2 hormone tests. All visits after Day 1 during the glucocorticoid stable period and the glucocorticoid reduction period have a visit window of +5 days; all visits during the glucocorticoid optimization period have a visit window of ±5 days.

[b] Option of at-home visit or at the study site.

[c] Within 1 week after Weeks 4, 6, and 10, if a glucocorticoid dose reduction occurred, the study site will call the subject for a safety follow-up. If needed, the subject may come in for an unscheduled visit to perform a safety follow-up (eg, vital signs, laboratory assessments).

[d] On Day 1, subjects will review applicable portions of the informed consent form as a reminder about the placebo-controlled design of the study. At Week 4, subjects will review applicable portions of the informed consent form as a reminder that glucocorticoid reduction period has started and about potential symptoms that they may experience.

[e] Includes measurement of waist circumference.

[f] After vital signs are obtained, measure blood pressure (single measurement) and heart rate again after the subject has been standing (from a seated position) for approximately 2 minutes. Compare the standing blood pressure vs the average of the 3 sitting blood pressures for evaluation of orthostasis criteria. Repeat once if abnormal (systolic blood pressure decrease >20 mm Hg, or diastolic blood pressure decrease >10 mm Hg).

[g] Including height (screening only). Measure blood pressure 3 times, in up to 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Height and weight will be measured with subjects not wearing shoes; weight will be measured with subjects not wearing outerwear (eg, jackets or coats).

[h] For all females of childbearing potential. Serum pregnancy testing at screening, urine pregnancy tests at other visits.

[i] Collect blood sample for hormone measurements (adrenocorticotropic hormone [ACTH], 17-hydroxyprogesterone [17-OHP], cortisol, androstenedione, testosterone, luteinizing hormone [LH], follicle stimulating hormone [FSH], progesterone, plasma renin activity [PRA; measured upright], and sex hormone binding globulin [only for the second blood sample collected at Day 1, Weeks 4 and 24]) in the morning approximately 2 to 3 hours after the morning glucocorticoid dose. At Day 1, Weeks 4 and 24, collect additional blood sample prior to morning glucocorticoid dose. The second blood sample should be collected prior to 1100 hours. Subjects not on a morning glucocorticoid should still have 2 morning blood samples taken (with the glucose tolerance test and/or before and after the morning study drug dose). The last dose of glucocorticoid taken prior to the first blood sample should be documented.

[j] Urine sample should be collected by the subject at home starting at midnight the night before the visit until the first morning void after awakening for the day using a container provided to the subject and brought to the study center.

[k] Collect blood sample after subject fasting at least 8 hours for glucose, insulin, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, and glycated hemoglobin (HbA1c).

[l] Collect blood sample for osteocalcin, bone-specific alkaline phosphatase, and C-terminal telopeptide (CTx) and collect urine sample (fasting, after first morning void) for N-terminal telopeptide (NTx).

[m] After an overnight fast (minimum of 8 hours), collect blood samples prior to (within 30 minutes) and approximately 2 hours after 75-gram glucose load (only in subjects without diabetes mellitus).

[n] For males only.

[o] For female subjects only. Menstrual questionnaire only for females of childbearing potential not on hormonal or intrauterine device contraceptives.

[p] Subjects should hold morning study drug dose (except Day 1) and morning glucocorticoid dose (unless not on a morning glucocorticoid). Study drug (except Day 1) and morning glucocorticoid dose (unless not on a morning glucocorticoid) will be taken at study site with breakfast (except Day 1 and Week 24, taken with glucose load). Collect blood samples prior to and approximately 2 hours after dosing at study site.

[q] Subjects will return all unused study drug, and a compliance check will be performed by counting the capsules returned at each study visit.

Table 2: Schedule of Assessments – Open-Label Treatment Period and Double-Blind Active-Controlled Treatment Period

Assessment	Open-Label Treatment Period[a]						Open-Label or Double-Blind Active-Controlled Treatment Period[a]				Follow-Up Period for subjects who do not enter the OLE
	Phone call	Month 7[b,c]	Month 8[c]	Month 9[b,c]	Month 10[b]	Month 12	Month 13[c,d]	Month 14[b,c]	Month 16[b,c]	Month 18/ET[e]	Month 19[a,e]
Physical exam[f]			X			X				X	X
Orthostatics[g]			X	X	X			X[d]	X[d]		
Vital signs and weight[h]		X	X	X	X	X	X	X	X	X	X
Chemistry labs			X	X	X	X		X	X	X	X
Hematology/coagulation		X	X			X	X	X	X	X	X
Urinalysis			X			X				X	X
PK blood sample		X	X	X	X	X	X	X	X	X	X
Pregnancy test[i]		X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Hormone panel[j]		X	X	X	X	X	X	X	X	X	X
TSH and free T4						X				X	
Urine androgen[k]						X	X			X	
Fasting metabolic panel[l]						X				X	
Bone markers[m]						X				X	
Glucose tolerance test[n]						X					
Testicular ultrasound[o]						X				X	
DXA[p]						X				X	
SF-36						X				X	
EQ-5D-5L						X				X	
MAF						X				X	
MOS-12						X				X	
PGWBI						X				X	
BPRS						X				X	X
C-SSRS		X	X	X	X	X		X	X	X	X
Hirsutism and Acne Scales[q]			X			X	X			X	X
Menstrual Questionnaire[q]		X	X	X	X	X	X	X	X	X	X
12-lead ECG			X			X	X			X	X
Potential GC reduction		X	X	X			X	X[d]	X[d]		
Onsite dosing[r]						X	X			X	
Dispense study drug			X		X	X		X	X		
Study drug accountability[s]			X		X	X		X	X	X	
AE monitoring	X	X	X	X	X	X	X	X	X	X	X
Prior & concomitant medications		X	X	X	X	X	X	X	X	X	X

AE=adverse event; BPRS=Brief Psychiatric Rating Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; DXA=dual-energy X-ray absorptiometry; ECG=electrocardiogram; ET=early termination; FSH=follicle stimulating hormone; GC=glucocorticoid; HbA1c=glycated hemoglobin; I/E=inclusion/exclusion; M12=Month 12; MAF=Multidimensional Assessment of Fatigue; MOS-12=Medical Outcomes Study 12-item Sleep Scale; PGWBI=Psychological General Well-Being Index; PK=pharmacokinetics; PRA=plasma renin activity; SF-36=36-Item Short Form Health Survey; T4=thyroxine; TSH=thyroid stimulating hormone.

[a] During the open-label or double-blind active-controlled treatment period, visits from Month 7 to Month 10 have a visit window of ±5 days and visits from Month 12 to Month 18 have a visit window of ±7 days. The Month 19 (if applicable) visit has a visit window of +7 days.
[b] At home or study site.
[c] Within 1 week after the visits at Months 7, 8, 9, 13 (only for re-randomized subjects), 14 (only for re-randomized subjects), and 16 (only for re-randomized subjects), if a glucocorticoid dose reduction occurred, the study site will call the subject for a safety follow-up. If needed, the subject may come in for an unscheduled visit for a safety follow-up (eg, vital signs, laboratory assessments).
[d] Only for re-randomized subjects.
[e] For subjects who discontinue the study prior to Month 18, assessments will be performed at the ET visit and at the follow-up visit (a follow-up visit is not required if the last dose of study drug was at least 28 days prior to the ET visit). Subjects who complete the Month 18 visit and elect to not enter the OLE will undergo a follow-up visit approximately 28 days after last dose of study drug.
[f] Includes measurement of waist circumference.
[g] After vital signs are obtained, measure blood pressure (single measurement) and heart rate again after the subject has been standing (from a seated position) for approximately 2 minutes. Compare the standing blood pressure vs the average of the 3 sitting blood pressures for evaluation of orthostasis criteria. Repeat once if abnormal (systolic blood pressure decrease >20 mm Hg, or diastolic blood pressure decrease >10 mm Hg).
[h] Measure blood pressure 3 times, in up to 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Height and weight will be measured with subjects not wearing shoes; weight will be measured with subjects not wearing outerwear (eg, jackets or coats).
[i] For all females of childbearing potential.
[j] Collect blood sample for hormone measurements (adrenocorticotropic hormone [ACTH], 17-hydroxyprogesterone [17-OHP], cortisol, androstenedione, testosterone, luteinizing hormone [LH], follicle stimulating hormone [FSH], progesterone, plasma renin activity [PRA; measured upright], and sex hormone binding globulin [only for the second blood sample collected at Months 12, 13, and 18]) in the morning approximately 2 to 3 hours after the morning glucocorticoid dose. At Month 12, Month 13 (only for re-randomized subjects), and Month 18/early termination, collect additional blood sample prior to morning glucocorticoid dose. The second blood sample should be collected prior to 1100 hours. Subjects not on a morning glucocorticoid should still have 2 morning blood samples taken (with the glucose tolerance test and/or before and after the morning study drug dose). The last dose of glucocorticoid taken prior to the first blood sample should be documented.
[k] Urine sample should be collected by the subject at home starting at midnight the night before the visit until the first morning void after awakening for the day using a container provided to the subject and brought to the study center.
[l] Collect blood sample after subject fasting at least 8 hours for glucose, insulin, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, and glycated hemoglobin (HbA1c).
[m] Collect blood sample for osteocalcin, bone-specific alkaline phosphatase, and C-terminal telopeptide (CTx) and collect urine sample (fasting, after first morning void) for N-terminal telopeptide (NTx).
[n] After an overnight fast (minimum of 8 hours), collect blood samples prior to (within 30 minutes) and approximately 2 hours after 75-gram glucose load (only in subjects without diabetes mellitus).
[o] For males only. Testicular ultrasound is not required during an early termination visit if the subject had a testicular ultrasound within 3 months prior.
[p] Not required during an early termination visit if the subject had a DXA within 3 months prior.
[q] For female subjects only. Menstrual questionnaire only for females of childbearing potential not on hormonal or intrauterine device contraceptives.
[r] Subjects should hold morning study drug dose and morning glucocorticoid dose (unless not on a morning glucocorticoid). Study drug and morning glucocorticoid dose (unless not on a morning glucocorticoid) will be taken at study site with breakfast (except Month 12, taken with glucose load [only in subjects without diabetes mellitus]). Collect blood samples prior to and approximately 2 hours after dosing at study site.
[s] Subjects will return all unused study drug, and a compliance check will be performed by counting the capsules returned at each study visit.

Table 3: Schedule of Assessments – Open-Label Extension Treatment Period (OLE; Month 18 Onwards) and Follow-Up Period

Assessment	OLE Treatment Period[a]					OLE Follow-Up Period[a]
	Month 18[b,d]	Month 21[c,d]	Month 24 and every 12 months thereafter[d]	Month 30 and every 12 months thereafter[d]	OLE ET	Final Study Visit (last dose of study drug + 4 weeks)
Informed consent[b]	X					
Physical exam[e]			X	X	X	X
Vital signs and weight[f]		X	X	X	X	X
Chemistry labs		X	X	X	X	X
Hematology/coagulation			X	X	X	X
Urinalysis			X	X	X	X
Pregnancy test[g]		X (u)	X (u)	X (u)	X (u)	X (u)
Hormone panel[h]		X	X	X	X	X
Fasting metabolic panel[i]			X			
Glucose tolerance test[j]			X			
Testicular ultrasound[k]			X		X[k]	
DXA			X		X[l]	
SF-36			X		X	
EQ-5D-5L			X		X	
MAF			X		X	
BPRS			X		X	X
C-SSRS		X	X	X	X	X
Hirsutism and Acne Scales			X	X	X	X
Menstrual Questionnaire[m]		X	X	X	X	X
Potential GC or crinecerfont dose adjustment[n]	X	X	X	X		
Onsite dosing[o]			X			
Dispense study drug[p]	X	X	X	X		
Study drug accountability[p]		X	X	X	X	
AE monitoring		X	X	X	X	X
Prior & concomitant medications		X	X	X	X	X

AE=adverse event; BPRS=Brief Psychiatric Rating Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; DXA=dual-energy X-ray absorptiometry; ECG=electrocardiogram; ET=early termination; FSH=follicle stimulating hormone; GC=glucocorticoid; HbA1c=glycated hemoglobin; I/E=inclusion/exclusion; MAF=Multidimensional Assessment of Fatigue; OLE=open-label extension treatment period; PK=pharmacokinetics; PRA=plasma renin activity; SF-36=36-Item Short Form Health Survey.

[a] All visits after Month 18 have a visit window of ±14 days, except the Final Study Visit has a visit window of +14 days.

[b] At Month 18, subjects will review applicable portions of the informed consent form and confirm participation in the optional OLE and should also complete all Month 18 assessments from the Open-Label or Double-Blind Active-Controlled Treatment Period (see Table 2).
[c] At home or study site.
[d] Within 1 week after any glucocorticoid dose reduction, the study site will call the subject for a safety follow-up. If needed, the subject may come in for an unscheduled visit for a safety follow-up (eg, vital signs, laboratory assessments).
[e] Includes measurement of waist circumference.
[f] Measure blood pressure 3 times, in at least 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Height and weight will be measured with subjects not wearing shoes; weight will be measured with subjects not wearing outerwear (eg, jackets or coats).
[g] For all subjects of childbearing potential.
[h] Collect blood sample for hormone measurements (adrenocorticotropic hormone [ACTH], 17-hydroxyprogesterone [17-OHP], cortisol, androstenedione, testosterone, luteinizing hormone [LH], follicle stimulating hormone [FSH], progesterone, plasma renin activity [PRA; measured upright], and sex hormone binding globulin [only for the second blood sample collected at Month 24 and every 12 months thereafter]) in the morning approximately 2 to 3 hours after the morning glucocorticoid dose. At Month 24 and every 12 months thereafter, collect additional blood sample prior to morning glucocorticoid dose. The second blood sample should be collected prior to 1100 hours. Subjects not on a morning glucocorticoid should still have 2 morning blood samples taken (with the glucose tolerance test and/or before and after the morning study drug dose). The last dose of glucocorticoid taken prior to the first blood sample should be documented.
[i] Collect blood sample after subject fasting at least 8 hours for glucose, insulin, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, and glycated hemoglobin (HbA1c).
[j] After an overnight fast (minimum of 8 hours), collect blood samples prior to (within 30 minutes) and approximately 2 hours after 75-gram glucose load (only in subjects without diabetes mellitus).
[k] For subjects with testes only. Testicular ultrasound is not required for an early termination visit if the subject had a testicular ultrasound within 3 months prior.
[l] DXA is not required for an early termination visit if the subject had a DXA within 3 months prior.
[m] Menstrual questionnaire only for subjects of childbearing potential not on hormonal or intrauterine device contraceptives.
[n] Appendix C, Open-Label Extension Treatment Period Glucocorticoid and Crinecerfont Dose Adjustment Guidance.
[o] Subjects should hold morning study drug dose (unless not on a morning study drug) and morning glucocorticoid dose (unless not on a morning glucocorticoid). Study drug (unless not on a morning study drug) and morning glucocorticoid dose (unless not on a morning glucocorticoid) will be taken with a glucose load (only in subjects without diabetes mellitus). Collect blood samples prior to and approximately 2 hours after dosing at study site.
[p] Study drug will be dispensed every 3 months. Subjects will return all unused study drug, and a compliance check will be performed by counting the capsules returned at each study visit.

9.2. Screening and Baseline Assessment

9.2.1. Cytochrome P450 21A2 Genotyping

On Day 1, a blood sample will be collected and stored for CYP21A2 status genotyping (only for subjects who have not previously had genotyping or are not able to provide records of prior genotyping). Genotyping blood samples collected from enrolled subjects will be shipped to a central laboratory for analysis.

9.2.2. Other Screening Assessments

Thyroid stimulating hormone: A thyroid stimulating hormone level will be measured at screening.

Urine Drug Screen: A urine sample will be tested for amphetamines, barbiturates, benzodiazepines, cocaine, phencyclidine, and opiates.

9.3. Efficacy Assessments

9.3.1. Glucocorticoid Dosing and Dose Reduction

Each subject will record their daily glucocorticoid regimen in the eDiary beginning at Screening Visit 1, including specific type of glucocorticoid and all doses taken each day for their usual regimen as well as any additional or sick-day dosing (Appendix B). The usual daily regimen will be converted to hydrocortisone equivalents (mg/m^2/day) adjusted for BSA (see Appendix A).

Guidelines for reducing or optimizing glucocorticoid dose should be followed in order to evaluate the efficacy of the study drug, except in the event that a subject requires sick-day dosing. Sick-day dosing may follow guidelines outlined in Appendix B or be based on guidance provided by the investigator or their treating physician. If a subject's glucocorticoid regimen is adjusted due to sick-day guidelines, the subject should resume their glucocorticoid dosing regimen (according to their glucocorticoid reduction schedule) for at least 3 days before their next scheduled hormone panel assessment. Of note, this 3-day window supersedes all other visit windows.

Glucocorticoid Dose Reduction during Placebo-Controlled Period

The goal of the glucocorticoid dose reduction period from Week 4 to Week 12 is to reach the subject's target physiologic dose of 8 to 10 mg/m^2/day (hydrocortisone equivalents adjusted for BSA) within 4 or fewer steps by Week 12, unless the subject has any signs or symptoms suggestive of clinically relevant glucocorticoid insufficiency or unacceptable symptoms of hyperandrogenism, as outlined below. However, before the glucocorticoid dose reduction is stopped for symptoms or signs of orthostatic hypotension, volume status should be optimized (eg, with additional dietary salt, salt tablets, intravenous saline).

- Unexplained hyponatremia (serum sodium <135 mmol/L)
- Orthostatic hypotension with decrease in systolic blood pressure >20 mmHg or in diastolic blood pressure >10 mmHg after standing (from a seated position) after

approximately 2 minutes, or severe symptoms of dizziness or lightheadedness upon standing

- Severe nausea, food aversion, vomiting
- Unacceptable symptoms of hyperandrogenism (eg, hirsutism, acne, amenorrhea)

Transient elevations in androstenedione in the absence of symptoms are not a reason for stopping the glucocorticoid dose reduction. It is expected that subjects may experience symptoms such as fatigue, nausea, abdominal discomfort, joint aches, etc, especially as doses are decreased towards the physiologic range. Subjects should be advised of this possibility and should contact the investigator if the symptoms become severe or prolonged.

A glucocorticoid dose of 8 mg/m^2/day (hydrocortisone equivalents) provides systemic cortisol at approximately 70th percentile of normal glucocorticoid production rate (Linder et al.,1990). The use of this replacement dosage has not been associated with glucocorticoid insufficiency in prior studies of patients with classic CAH (Merke et al., 2000).

Based on the subject's starting and target glucocorticoid doses, the investigator will have a detailed schedule for the glucocorticoid dose reduction that will occur between Weeks 4 and 12. Details of the subject's baseline glucocorticoid regimen and dose reduction schedule will be submitted for Sponsor review prior to randomization. Specific standardized schedules for commonly used glucocorticoid dosing regimens will be provided in the study reference manual. Guidance will be provided for the glucocorticoid dose reduction schedule if a standardized schedule is not available for a subject's baseline glucocorticoid regimen. This schedule may include specific details (for each of the dose reduction steps) such as the total daily dose of each glucocorticoid (if more than 1 type of glucocorticoid taken), the breakdown of doses over the course of the day (eg, morning, afternoon, evening), and the exact number of pills at each dosage strength to be taken at each time during the day, including whether splitting of tablets is required or liquid formulations are used. If splitting of tablets is needed during glucocorticoid dose adjustments, using a smaller dosage strength (if available) in order to avoid quartering of tablets is recommended. In addition, it is recommended that the same formulation (liquid or tablet) of a given glucocorticoid be used during the glucocorticoid dose reduction as used at baseline.

The dose reduction schedule should follow the guideline of first decreasing the most non-physiologic glucocorticoid type and timing (specifically if on dexamethasone, this should be reduced or titrated off first, and if on bedtime or evening glucocorticoid, this should be reduced or titrated off first). The glucocorticoid dose reduction should generally be performed in 4 steps, but may be performed in fewer steps based on the subject's starting glucocorticoid dose and availability of glucocorticoid dosage strengths. At the final step of the glucocorticoid dose reduction, the subject should be receiving a physiologic dose of glucocorticoids (ie, 8 to 10 mg/m^2/day in hydrocortisone equivalents adjusted for BSA). The target range of 8 to 10 mg/m^2/day allows for inexactness due to currently available glucocorticoid dosage forms. In the event that a glucocorticoid dose cannot be feasibly achieved between 8 to 10 mg/m^2/day due to available dosage strengths, it is acceptable to alternate doses such that the average dose over 2 consecutive days is within the target range. The glucocorticoid dose reduction schedule will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents adjusted for BSA,

although doses below 8 mg/m^2/day are permitted if the investigator feels this is clinically indicated and acceptable.

At the Week 12 visit, based on review of the subject's hormone levels collected up to that visit as well as based on clinical assessment, the investigator will determine the appropriate dose of glucocorticoid to continue past Week 12 (the reduced dose if tolerated, or a prior higher dose) in order to achieve adequate control of androgen levels (ie, androstenedione ≤120% of baseline or ≤ULN for age and sex).

Glucocorticoid Dose Optimization during Placebo-Controlled Period

The goal of the glucocorticoid dose optimization period from Week 12 to Week 24 is to maintain glucocorticoid dose stable at the dose determined at Week 12 to the extent possible. However, at Weeks 16 and 20, the investigator should adjust the subject's glucocorticoid dose as needed with the goal of reaching the glucocorticoid dose (lowest dose possible) at Week 24 that will achieve control of androgen levels as defined above.

Glucocorticoid Dose Reduction during Open-Label Treatment Period

Subjects who are still at a glucocorticoid dose >11 mg/m^2/day (hydrocortisone equivalents adjusted for BSA) by Month 7 should attempt to reduce their glucocorticoid dose again after completing the first month (glucocorticoid stable period) of open-label treatment (with the goal to achieve a target physiologic dose of 8 to 10 mg/m^2/day [hydrocortisone equivalents adjusted for BSA] by Month 10), unless the investigator deems further attempts at dose reduction to not be advisable for that subject.

The goal of the glucocorticoid dose reduction period from Month 7 to Month 10 is to reduce glucocorticoid doses by 10% to 20% at each of the visits at Months 7, 8, and 9 (until the target dose of 8 to 10 mg/m^2/day is reached) while maintaining control of androgens, as would normally be done in routine clinical practice. Glucocorticoid doses should be reduced at Months 7, 8, and 9 as long as androstenedione level is in adequate control, and the subject is not experiencing unacceptable symptoms or any signs or symptoms suggestive of clinically relevant glucocorticoid insufficiency. The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day in hydrocortisone equivalents adjusted for BSA, although doses below 8 mg/m^2/day are permitted if the investigator feels this is clinically indicated and acceptable.

At Month 12, subjects who have reduced glucocorticoid dose to ≤11 mg/m^2/day will continue on the open-label study drug 100 mg bid and continue on glucocorticoid therapy with the goal to maintain dose stable to the extent possible while maintaining adequate control of androgen levels (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex). However, the glucocorticoid dose can be adjusted based on routine clinical care.

Glucocorticoid Dose Reduction during Double-Blind, Active-Controlled Treatment Period

At Month 12, subjects with glucocorticoid dose >11 mg/m^2/day will be re-randomized to continue active study drug at 100 mg bid or adjust their active study drug dose to 100 mg qAM and 200 mg qPM (study drug will be blinded such that all re-randomized subjects will be taking the same number of capsules). After a 1-month period of stable glucocorticoid regimen (except for sick-day guidelines), subjects should attempt to reduce their glucocorticoid dose starting at Month 13 with the goal to achieve a target physiologic dose of 8 to 10 mg/m^2/day by Month 18

while maintaining adequate control of androgen levels (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex), unless the investigator deems further attempts at dose reduction to not be advisable for that subject. Glucocorticoid doses should be reduced by 10% to 20% at each of the visits at Months 13, 14, and 16 until the target dose of 8 to 10 mg/m^2/day is reached as long as the subject is not having signs or symptoms suggestive of clinically relevant glucocorticoid insufficiency (as would normally be done in routine clinical practice) and as long as androstenedione levels are controlled (ie, androstenedione ≤120% of the subject's baseline or ≤ULN for age and sex). The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents adjusted for BSA, although doses below 8 mg/m^2/day are permitted if the investigator feels this is clinically indicated and acceptable. After each of the glucocorticoid dose reduction steps, the site should contact the subject by telephone (within a week) to assess how the subject is tolerating the glucocorticoid dose reduction.

Glucocorticoid Dose Reduction during Open-Label Extension Treatment Period

During the OLE, subjects may have their glucocorticoid doses adjusted as appropriate and tolerated to achieve the lowest glucocorticoid dose that maintains adequate disease control (in the opinion of the investigator). The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents. After each glucocorticoid dose reduction, the site should contact the subject by telephone (within a week) to assess how the subject is tolerating the glucocorticoid dose reduction.

Starting at Month 18, all subjects who are continuing in the OLE will initially receive open-label crinecerfont 100 mg bid. If the subject has inadequate disease control despite receiving glucocorticoid treatment at their target dose (in the opinion of the investigator), the crinecerfont dose may be increased to 100 mg qAM and 200 mg qPM (including at Month 18, after laboratory results are available). If the increased dose of 100 mg qAM and 200 mg qPM is not well tolerated, the dose may be reduced back to 100 mg bid. After the Month 24 visit, an alternative dosing regimen of once daily 200 mg qPM can be considered per the investigator (Appendix C). Crinecerfont doses should generally only be adjusted at or shortly after study visits (after laboratory results are available).

In the setting of inadequate disease control, if the glucocorticoid dose is at or above the target, an increase in the glucocorticoid dose should generally be considered only after the crinecerfont dose has been maximized for the subject. Changes to the glucocorticoid and crinecerfont doses should generally be separated by at least 1 month in order to assess the effect of each change.

9.3.2. Hormone Panel

At all study visits (including screening) except Week 8 and Week 10, a blood sample should be collected for hormone measurements in the morning approximately 2 to 3 hours after the morning glucocorticoid dose (and fludrocortisone dose if taking) is taken. Additional blood samples for hormone measurements may be collected at unscheduled visits if clinically indicated.

In addition, a predose blood sample for hormone measurements prior to the morning glucocorticoid dose (and fludrocortisone dose if taking) will be collected at Day 1 (baseline),

Weeks 4 and 24, and Months 12, 13 (for subjects re-randomized at Month 12), 18, 24, and every 12 months thereafter. At these visits, subjects will hold their morning glucocorticoid dose until arriving at the study site so that a blood sample for hormone measurements can be collected. Subjects will then take their morning dose of glucocorticoid (and fludrocortisone dose if taking) at the study site, with another blood sample collected approximately 2 hours later. The second (2-hr postdose) blood sample should be collected prior to 1100 hours. Subjects not on a morning glucocorticoid should still have 2 morning blood samples taken (eg, with the glucose tolerance test at Day 1, Week 24, Month 12, etc.; and/or before and 2 hours after the morning study drug dose). Additional plasma or serum hormone levels may be evaluated using the second blood sample collected at these timepoints.

The hormone panel will include assessment of:

- Adrenal androgens and precursors (ACTH, 17-OHP, cortisol, androstenedione, testosterone) and sex hormone binding globulin (only for the second blood sample collected at Day 1, Weeks 4 and 24, and Months 12, 13, 18, 24, and every 12 months thereafter)
- Reproductive function (luteinizing hormone [LH], FSH, progesterone)
- Mineralocorticoid status (upright PRA)

The blood samples will be processed and stored according to the procedure as specified in the laboratory manual.

9.3.3. Urine Androgen Metabolite Levels

Urine androgen metabolite levels (eg, androsterone, etiocholanolone) will be measured to provide an assessment of the early morning surge in ACTH secretion and downstream androgen production. Urine samples will be collected by each subject at home starting at midnight the night before until the first morning void after awakening for the day on Day 1 (baseline), Weeks 4 and 24, Months 12, 13 (for subjects re-randomized at Month 12), and 18, and at early termination, if early termination occurs prior to Month 18. If the subject does not need to void after midnight until the following morning, only the first void in the morning upon waking needs to be collected. If the subject needs to void during the night, all voids after midnight until the first void in the morning upon waking for the day should be collected. Supplies for collecting urine sample(s) will be provided to the subject. The urine sample should be brought to the site for the study visit and will be processed and stored according to the procedure as specified in the laboratory manual.

9.3.4. Metabolic Assessments

Chronic supraphysiologic glucocorticoid dosing can lead to metabolic abnormalities such as insulin resistance, glucose intolerance, diabetes mellitus, and dyslipidemia.

Fasting blood tests (after an overnight fast, minimum 8 hours) will be obtained at Day 1, Week 24, Month 12, Month 18, Month 24, and every 12 months thereafter:

- Fasting lipid panel - total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides

- Fasting glucose and insulin for calculation of the homeostatic model assessment of insulin resistance (HOMA-IR) index (fasting insulin [µIU/L] × fasting glucose [mg/dL] divided by 405)
- Glycated hemoglobin (HbA1c)

In subjects without diabetes mellitus, a standard 75-gram glucose tolerance test will be performed at Day 1, Week 24, Month 12, Month 24, and every 12 months thereafter, after an overnight fast (minimum 8 hours) with blood samples collected prior to (within 30 minutes of) the 75-gram glucose load and approximately 2 hours after the glucose load.

9.3.5. Testicular Ultrasound

Testicular ultrasounds will be performed to detect adrenal rest tissue in all male subjects. The entire testicle should be scanned thoroughly and at least 3 transverse and axial images will be captured. The location, size, shape, boundary and echogenicity of any TARTs should be determined. In addition, testicular size/volume (approximately ½× [height × width × length]) should be recorded as well as the presence or absence of the testicular mediastinum. Ultrasound data will be sent to a central imaging facility for evaluation. In addition, data from the report based on the local radiologist's reading should be entered in the appropriate eCRF.

Testicular ultrasounds will be performed on Day 1, Week 24, Month 12, Month 18, Month 24, and every 12 months thereafter; additional assessments may be obtained if clinically indicated. Testicular ultrasound is not required for an early termination visit if the subject had a testicular ultrasound within 3 months prior. From Day 1 to Month 18, testicular ultrasounds may be performed up to 7 days prior to the actual visit date. After Month 18, testicular ultrasound may be performed up to 14 days prior to the actual visit date at Month 24 and every 12 months thereafter. The time window for a testicular ultrasound that needs to be repeated due to an inadequate initial scan is within 2 weeks of the actual visit date (including Day 1).

9.3.6. Hirsutism and Acne Scales

Visual analog scales will be used to assess the subject’s perception of severity of hirsutism and acne in in all female subjects. Subjects will score their hirsutism and acne on a 100 mm visual analog scale, from 0 mm (no symptoms) to 100 mm (very severe symptoms).

The Hirsutism and Acne Scales will be administered on Day 1 (baseline), Weeks 4, 12, and 24, and Months 8, 12, 13, 18, 24, and every 6 months thereafter. It will also be administered at early termination and at the Follow-Up Visit.

9.3.7. Menstrual Cycle Questionnaire

The Menstrual Cycle Questionnaire will be used to assess regularity of menstrual cycles in female subjects of childbearing potential who are not on hormonal or IUD contraceptives. Subjects will be asked to document the date and amount of flow for each day of their menstrual cycles in the eDiary beginning at Screening Visit 1.

Instructions for completing the Menstrual Cycle Questionnaire will be reviewed at Screening Visit 1. Subject documentation of menstrual cycle information collected in the eDiary will be reviewed by the site at Day 1, Weeks 4, 9, 12, 16, and 24, and Months 7, 8, 9, 10, 12, 13

(for subjects re-randomized at Month 12), 14, 16, 18, 21, 24, and every 6 months thereafter (except unscheduled). It will also be reviewed at early termination and at the Follow-Up Visit. Missing or unclear information should be clarified with the subject.

9.3.8. Dual Energy X-Ray Absorptiometry

A dual-energy X-ray absorptiometry (DXA) scan will be performed to assess bone mineral density and body composition. All DXA scans will be acquired locally using a Lunar or Hologic instrument (the same machine should be used throughout the study for a given subject) and will be sent to a central imaging facility for evaluation. A single scan of the femur and spine will be conducted for assessment of bone mineral density at the lumbar spine, total hip, and femoral neck. A whole-body scan will be performed for measurement of body composition (fat mass, lean mass, total body mass) and total bone mineral content and bone mineral density. DXA scans will be performed according to standardized procedures by trained technicians. A study procedure manual will be provided by the central imaging facility that will include all DXA related acquisition and submission details.

Subjects should refrain from taking any calcium supplements for 24 hours before the DXA scans. In addition, subjects who have had procedures using contrast agents (eg, iodine, barium or nuclear medicine isotope) within 7 days before a scheduled DXA scan will be scanned after the contrast agent has cleared (approximately 7 days after administration).

Pregnancy tests should be performed prior to the DXA scan. Additionally, before a DXA scan is performed, the DXA technician will ask the subject if there is any chance that she is pregnant. If there is, the scan should be postponed until pregnancy is ruled out (urine pregnancy test is required).

DXA will be performed at Day 1 (baseline), Week 24, Month 12, Month 18, Month 24, and every 12 months thereafter. It will also be performed at early termination, if the subject has not had a DXA performed within the previous 3 months. From Day 1 to Month 18, DXA scans may be performed up to 7 days prior to the actual visit date. After Month 18, DXA scans may be performed up to 14 days prior to the actual visit date. The time window for a DXA scan that needs to be repeated due to an inadequate initial scan is within 2 weeks of the actual visit date (including Day 1).

9.3.9. Bone Marker Measurements

The following bone markers will be obtained at Day 1, Week 24, Month 12, Month 18, and at early termination, if early termination occurs prior to Month 18:

- Serum osteocalcin and bone-specific alkaline phosphatase to assess bone formation
- Serum C-terminal telopeptide (CTx) and urine N-terminal telopeptide (NTx) (collected after the first morning void, after an overnight fast) to assess bone resorption

9.4. Patient-Reported Outcomes

9.4.1. 36-Item Short Form Health Survey

The 36-Item Short Form Health Survey (SF-36) is a 36-item, self-administered questionnaire. It measures health on 8 dimensions: vitality, physical functioning, pain, general health perception, physical role limitations, emotional role functioning, social functioning, and mental health. The SF-36 has been shown to be a reliable and validated instrument (Brazier et al., 1992). Version 2 of the SF-36 will be used in this study.

The SF-36 will be administered on Day 1 (baseline), Week 24, Month 12, Month 18, Month 24, and every 12 months thereafter. It will also be administered at early termination.

9.4.2. EQ-5D-5L

The EQ-5D-5L is a general, single index measure for describing and valuing health (Herdman et al., 2011). It defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The subject indicates his/her health state by checking the box next to the most appropriate statement. The scores for the 5 dimensions can be combined into a 5-digit number that describes the subject's health state. Subjects also rate their overall health on a 0 to 100 hash-marked, vertical visual analogue scale (EQ-VAS), where 100 is labeled 'The best health you can imagine' and 0 is labeled 'The worst health you can imagine.'

The EQ-5D-5L will be administered on Day 1 (baseline), Week 24, Month 12, Month 18, Month 24, and every 12 months thereafter. It will also be administered at early termination.

9.4.3. Multidimensional Assessment of Fatigue

The Multidimensional Assessment of Fatigue (MAF) is a 16-item scale that measures fatigue according to 4 dimensions: degree and severity, distress that it causes, timing of fatigue (over the past week, when it occurred and any changes), and its impact on various activities of daily living (household chores, cooking, bathing, dressing, working, socializing, sexual activity, leisure and recreation, shopping, walking, and exercising) (Belza, 1995). Subjects rate each item 1 through 14 using a 10-point numeric rating scale, and items 15 and 16 using categorical responses for timing. The MAF has established reliability and validity across a number of patient samples in rheumatology, endocrinology, neurology, and cardiovascular disease (Belza et al., 2018).

The MAF will be administered on Day 1 (baseline), Week 24, Month 12, Month 18, Month 24, and every 12 months thereafter. It will also be administered at early termination.

9.4.4. Psychological General Well-Being Index

The Psychological General Well-Being Index (PGWBI) is a validated 22-item scale that assesses psychological and general well-being in 6 domains: anxiety, depressed mood, positive well-being, self-control, general health and vitality (Grossi et al., 2006). The scores for all domains can be summarized to provide a maximum score (up to 110 points).

The PGWBI will be administered on Day 1 (baseline), Week 24, and Months 12, and Month 18. It will also be performed at early termination, if early termination occurs prior to Month 18.

9.4.5. Medical Outcomes Study 12-Item Sleep Scale

The Medical Outcomes Study 12-item Sleep Scale (MOS-12) is a reliable, valid tool for assessing changes in the sleep (Allen et al., 2009). The MOS-12 is a subject-reported, non-disease-specific instrument for evaluating sleep outcomes and consists of 12 items to measure 6 sleep dimensions (initiation, quantity, maintenance, respiratory problems, perceived adequacy, and somnolence) (Smith and Wegener, 2003).

The MOS-12 will be administered on Day 1 (baseline), Week 24, and Months 12 and Month 18. It will also be administered at early termination, if early termination occurs prior to Month 18.

9.5. Pharmacokinetic Assessments

Blood samples for determination of plasma concentrations of crinecerfont and metabolites will be collected on Day 1 (baseline), Weeks 2, 4, 6, 9, 12, 16, 20, and 24, and Months 7, 8, 9, 10, 12, 13 (if subject re-randomized), 14, 16, 18; they will also be collected at early termination and at the Follow-Up Visit, if early termination occurs prior to Month 18. Only 1 blood sample for PK measurement will be collected at each visit; at Day 1, Weeks 4, 24, and Months 12, 13 (if subject re-randomized), and 18, this sample should be the one prior to the morning study drug dose. At all other visits, the blood sample for PK measurement should be collected at approximately the same time of the morning throughout the study.

For each sample, approximately 2 mL of blood will be collected in tubes containing EDTA K_2. The exact time of sampling in hours and minutes will be recorded for all PK plasma samples. A final PK sample should be collected from subjects who discontinue study drug dosing early.

The blood samples will be processed and stored according to the procedure as specified in the laboratory manual. Samples will be shipped on dry ice to the central laboratory for analysis.

9.6. Safety Assessments

Concomitant medication use and adverse events (AEs) will be monitored throughout the study as described in Section 9.9.1 and Section 11, respectively. Additional safety assessments are described in the following sections.

Subjects with results from safety assessments that are of potential clinical significance should receive appropriate medical evaluation. To accomplish this, the Investigator and the Medical Monitor will review each of these subject's laboratory, vital signs, ECG data, AE records, and any other pertinent sections of the eCRF. All correspondence related to the subject will be documented. For any abnormal safety assessment deemed clinically significant, the investigator will perform appropriate follow-up assessments (eg, repeat analysis), until the cause of the abnormality is determined and/or until the value returns to baseline (or within normal limits), or the investigator deems the abnormality to be of no clinical significance.

Appropriate psychiatric evaluation and intervention will be provided for any treatment-emergent suicidal behavior or clinically significant suicidal ideation.

9.6.1. Specific Monitoring Considerations

Based on the available safety data to date, there are no identified risks with crinecerfont administration, and thus no standardized or specific monitoring protocols are warranted. In general, all AEs, including those related to clinically significant changes in laboratory results, ECGs, or physical examination findings must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated.

Section 9.10.1 specifies 2 situations under which study drug dosing must be discontinued:

- QTcF value >500 msec (cardiologist verified) on any ECG tracing.
- If the subject exhibits suicidal behavior or suicidal ideation of type 4 or 5 based on the C-SSRS.

In a prior 8-week Phase 2 study of crinecerfont in subjects with major depressive disorder, a slightly higher incidence of neutropenia was observed with the 100 mg dose (6.7%) compared to 20 mg (0.8%), 50 mg (2.5%), and placebo (1.7%) but similar to that of the active comparator escitalopram (4.3%). Events of neutropenia were based on laboratory findings and were generally mild (with absolute neutrophil count in the range of 1.0 to $<1.5 \times 1.0^3/mm^3$), transient (likely reflecting normal variability), and/or occurred in the setting of lower baseline values. In the Phase 2 study in adult CAH patients, there were no decreases in neutrophil count to $<1.5 \times 10^3/mm^3$. Based on the available data to date, there is no clear evidence to indicate that crinecerfont leads to the development of clinically relevant neutropenia. Potential subjects with absolute neutrophil count $<1.0 \times 10^3/mm^3$ will be excluded from participation in the study (Section 8.2). Complete blood count with differential will be monitored regularly during the study. Any abnormalities in neutrophil count should be assessed for clinical significance and reported as an AE if appropriate and monitored as outlined in the guidance above.

Patients with classic CAH have an inherent risk for adrenal crisis due to their underlying adrenal insufficiency and reliance on exogenously administered glucocorticoids, including the need to self-administer higher doses in situations of stress such as can occur with infection. Potential subjects who are assessed by the investigator as having an increased risk of developing adrenal crisis will be excluded from participation in the study (Section 8.2). Subjects will be required to be on a supraphysiologic glucocorticoid dose to participate in the study, and will have adjustment of their glucocorticoid dose with the goal to reduce to more physiologic doses while androstenedione control is maintained (Section 9.3.1). The upper end of the target glucocorticoid dose (8 to 10 $mg/m^2/day$) corresponds to the 90th percentile of normal cortisol production in healthy subjects based on stable isotope methodology (Purnell et al., 2004; Linder et al., 1990). Thus, the likelihood of causing glucocorticoid insufficiency by targeting doses in this range is considered low. Nevertheless, when reducing glucocorticoid doses (as appropriate while maintaining androgen control), investigators should monitor subjects closely with assessment of symptoms, orthostatic blood pressure, and clinical labs for any evidence of glucocorticoid insufficiency. Guidance is provided in Section 9.3.1 regarding the criteria for stopping further glucocorticoid dose reduction. In addition, subjects should follow sick-day glucocorticoid dosing

guidelines based on the investigator, their treating physician, or the guidelines provided in Appendix B.

While there is no evidence to support an increased risk of neuropsychiatric adverse effects, including suicidality, with crinecerfont administration, regular monitoring for suicidality and neuropsychiatric AEs will be performed with the C-SSRS (see Section 9.6.9) and Brief Psychiatric Rating Scale (BPRS; see Section 9.6.10) in the study, given that some studies have reported a higher prevalence of depression and/or anxiety in patients with classic CAH (Jenkins-Jones et al., 2018; Stewart et al., 2016; de Vries et al., 2019; Arlt et al., 2010), and data with chronic administration of crinecerfont in CAH patients is currently limited. Appropriate psychiatric evaluation and intervention will be provided for any treatment-emergent suicidal behavior or clinically significant suicidal ideation.

An independent DMC will further help to minimize and manage risks in this study to ensure the safety of study subjects by periodically reviewing unblinded clinical safety data, including laboratory, ECGs, vital signs, AEs, events requiring sick-day glucocorticoid dosing, C-SSRS, and BPRS data (see Section 9.6.2).

9.6.2. Data Monitoring Committee

An independent DMC will periodically review ongoing unblinded clinical and safety data to ensure the safety and well-being of the study subjects. The DMC consists of 5 members, including 4 physicians and a statistician with expertise in the areas of clinical trials, endocrinology, and biostatistics. Only members of the DMC have the authority and responsibility of voting on recommendations to the Sponsor for study conduct. The data review may result in recommendation for early termination of the study or changes to the protocol and informed consent based on unexpected adverse findings. The DMC will also evaluate results from the interim analysis and provide a recommendation to the Sponsor as described in Section 13.7. The DMC will convene its first data review meeting after approximately 30 subjects have completed the Week 4 visit and reconvene approximately every 4 to 6 months thereafter based on enrollment rate. Further details describing the responsibilities, timing of meetings, and data review procedures are included in the DMC charter.

9.6.3. Vital Sign Measurements Including Height and Weight

Vital sign measurements, including systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature (oral, axillary, tympanic or temporal artery), as well as body weight will be measured. Blood pressure and pulse rate will be measured 3 times, in up to 1-minute intervals, using a Sponsor-provided calibrated automatic blood pressure cuff (with the exception of at-home visits) after the subject has been sitting quietly for at least 5 minutes. Height and weight will be measured with subjects not wearing shoes; weight will be measured with subjects not wearing outerwear (eg, jackets or coats).

Vital sign measurements including weight will be obtained before any scheduled blood sample collection at screening, Day 1 (baseline), Weeks 4, 6, 9, 12, 16, 20, 24, and Months 7, 8, 9, 10, 12, 13 (for subjects re-randomized at Month 12), 14, 16, 18, 21, 24, and every 6 months thereafter. Vital signs will also be obtained at early termination and at the Follow-Up Visit. Height will be measured at screening only.

9.6.4. Medical History

A medical history will be taken at the screening visit and updated on Day 1 (baseline) and as needed throughout the study.

9.6.5. Orthostatics

Assessment of orthostatics will be performed as follows: after vital signs are obtained with blood pressure and heart rate measured after the subject has been sitting quietly for at least 5 minutes, blood pressure and heart rate will be measured again (single measurement) after the subject has been standing for approximately 2 minutes. Compare the standing blood pressure versus the average of the 3 sitting blood pressures for evaluation of orthostasis criteria. Repeat the standing blood pressure once if abnormal (systolic BP decrease >20 mm Hg, or diastolic BP decrease >10 mm Hg).

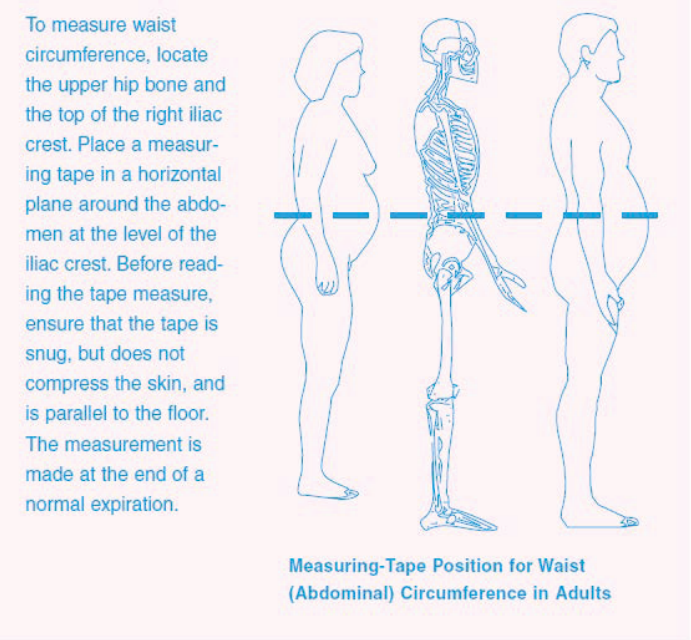
Orthostatics will be assessed at screening; Day 1; Weeks 6, 9, 12, and 24; Months 8, 9, and 10; Months 14 and 16 for subjects who are re-randomized.

9.6.6. Physical Examination

The complete physical examination will consist of an assessment of general appearance, skin and mucosae, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest/lungs, cardiovascular, abdomen, extremities, musculoskeletal, and neurological system.

Waist circumference will be measured as part of the physical examination. The measuring tape should be placed in a horizontal plane around the abdomen at the level of the iliac crest (Figure 3). Ensure that the tape is snug but does not compress the skin and is parallel to the floor. Obtain the measurement at the end of a normal expiration.

Figure 3: Waist Circumference Measurement



NHLBI, 2000.

A complete physical examination with measurement of waist circumference will be performed at screening, Day 1 (baseline), Weeks 4, 12, 24, and Months 8, 12, 18, 24, and every 6 months thereafter. It will also be performed at early termination and at the Follow-Up Visit.

9.6.7. Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has rested supine for at least 5 minutes. The ECG parameters that will be assessed include heart rate, PR interval, QRS duration, QT interval, and QTcF (machine readings or calculated). Additionally, the occurrence of de- and re-polarization and rhythm disorders or other abnormalities will be assessed. Based on the review of these parameters, the investigator or designee will note if the ECG is Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant. If the ECG is Abnormal Clinically Significant, the investigator or designee will provide a description of the abnormality recorded on the AE eCRF.

The 12-lead ECG will be conducted at screening, Day 1 (baseline), Weeks 4 and 24, and Months 8, 12, 13 (for subjects re-randomized at Month 12), and 18. For subjects who do not enter the OLE, it will also be conducted at early termination and at the Follow-Up Visit. ECGs should be performed within ±2 hours of morning study drug dosing (except at Day 1; on Day 1, the ECG should be conducted at approximately the same time of day that it will be conducted during the remainder of the study).

9.6.8. Clinical Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory. In addition, a urine pregnancy test will be performed by the study site on Day 1 to confirm subject eligibility. The central laboratory will provide instructions and supplies to the study staff before study initiation and instructions will be included in a laboratory manual. The laboratory test battery will include routine and screening laboratory tests.

The following clinical safety laboratory assays will be performed:

Hematology: complete blood count including WBC count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, and platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red cell distribution width (RDW), mean platelet volume (MPV).

Coagulation: aPTT, PT, INR

Clinical Chemistry: sodium, potassium, calcium, magnesium, phosphorus, chloride, blood urea nitrogen, bicarbonate, creatinine, uric acid, albumin, alkaline phosphatase, lactate dehydrogenase, AST, ALT, gamma-glutamyl transferase, creatine kinase, total bilirubin, total protein, and glucose.

Urinalysis: casts, crystals, specific gravity, nitrite, ketones, protein, urobilinogen, glucose, bilirubin, creatinine, leukocyte esterase, occult blood, and pH; microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive for nitrite, protein, leukocyte esterase, or blood.

Thyroid stimulating hormone (TSH) and free T4 levels: TSH and free T4 levels will be measured at screening (TSH only) and at scheduled timepoints during the study.

Pregnancy Test: Pregnancy tests will be performed throughout the study for female subjects of childbearing potential. A serum beta-human chorionic gonadotropin (β-hCG) pregnancy test will be performed at screening and a urine pregnancy test (using a urine pregnancy kit provided by the central laboratory) will be performed at and after Day 1 (baseline).

9.6.9. Columbia-Suicide Severity Rating Scale

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). There are versions of the questionnaire designed for use at screening (Baseline/Screening version) and at Day 1 and subsequent visits throughout the study (Since Last Visit version). All versions of the C-SSRS include a series of screening questions related to suicidal ideation and suicidal behavior. Subject responses of "yes" to one or more screening questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior. Subjects with any suicidal behavior within the past year or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) in the 6 months before screening based on the C-SSRS should be excluded (see exclusion criterion #15).

The C-SSRS will be administered and scored by the investigator or qualified study center personnel at screening, Day 1 (baseline), Weeks 4, 9, 12, 16, 20, and 24, and Months 7, 8, 9, 10, 12, 14, 16, 18, 21, 24, and every study visit thereafter. It will also be administered and scored at early termination and at the Follow-Up Visit. If a study visit is conducted at the subject's home, the site will administer the C-SSRS by telephone.

9.6.10. Brief Psychiatric Rating Scale

The Brief Psychiatric Rating Scale (BPRS) is a clinician-rated tool designed to assess the severity of psychopathology in subjects with schizophrenia and other psychotic disorders (Overall and Gorham, 1962; Overall and Gorham, 1988). The BPRS includes 18 items that address somatic concern, anxiety, emotional withdrawal, conceptual disorganization, guilt feelings, tension, mannerisms and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behaviors, motor retardation, uncooperativeness, unusual thought content, blunted affect, excitement, and disorientation. The severity of each of the 18 items of the BPRS is rated on a scale of 1 (not present) to 7 (extremely severe) (total score range: 18 to 126). Higher scores represent greater symptom severity.

The investigator or other qualified site personnel will administer and score the BPRS at screening, Day 1 (baseline), Weeks 12 and 24, and Months 12, 18, 24, and every 12 months thereafter. The BPRS will also be administered and scored at early termination and at the Follow-Up Visit.

9.7. Specific Study Period Information

9.7.1. Screening Period (Week -4 to Day -1)

9.7.1.1. Screening Visit 1

The following study procedures and assessments will be performed at Screening Visit 1:

- Obtain informed consent.
- Assess inclusion/exclusion criteria.
- Review and record medical history.
- Perform a physical examination including measurement of waist circumference.
- Perform vital signs (including height and weight) and orthostatics.
- Collect blood samples for TSH; serum pregnancy test (β-hCG) only for female subjects of childbearing potential; chemistry, hematology, and coagulation labs; hormone panel.
- Collect urine for urine drug screen and for urinalysis.
- Perform 12-lead ECG.
- Administer the BPRS and C-SSRS (Screening/Baseline version).
- Provide eDiary to record daily glucocorticoid doses.
- Review instructions for the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives) using the eDiary to document the date and amount of flow for each day of their menstrual cycles.
- AE monitoring.
- Record prior and concomitant medications.

9.7.1.2. Screening Visit 2: at home or study site

The following study procedure will be performed at Screening Visit 2 (scheduled approximately 2 weeks after Screening Visit 1):

- Collect blood sample for hormone panel.
- AE monitoring.

Subjects will be provided with urine collection supplies during the screening period.

9.7.2. Randomized, Double-Blind, Placebo-Controlled Treatment Period (Day 1 up to Week 24)

9.7.2.1. 4-Week Glucocorticoid Stable Period (Day 1 up to Week 4)

9.7.2.1.1. Baseline (Day 1)

Subjects will bring urine sample that was collected at home (all voids from midnight the night before the study visit to the first morning void after awakening for the day) as specified in Section 9.3.3. Subjects should arrive at the study site for the Day 1 (baseline) visit in the morning in a fasted state (minimum 8-hour fast) and prior to their morning dose of glucocorticoid. They should bring their morning dose of glucocorticoid to take at the study site after the first set of blood samples.

The following study procedures and assessments will be performed:

- Subjects will review applicable portions of the informed consent form (ICF) as a reminder about the placebo-controlled design of the study.
- Update inclusion/exclusion criteria as needed; subjects who continue to be eligible for the study will be randomized.
- Update medical history as needed.
- Perform a physical examination including measurement of waist circumference.
- Perform vital signs (including weight) and orthostatics.
- Collect blood samples for TSH and free T4; chemistry, hematology, and coagulation labs; PK; hormone panel (prior to and approximately 2 hours after morning dose of glucocorticoid); fasting metabolic panel; bone markers; and CYP21A2 genotyping.
- Perform glucose tolerance test (only in subjects without diabetes mellitus).
- Collect urine sample for urinalysis; urine NTx (fasting, after first morning void); and urine pregnancy test (only for female subjects of childbearing potential).
- Collect subject's at-home urine sample for urine androgen metabolites.
- Perform 12-lead ECG.
- Perform testicular ultrasound (males only).
- Perform DXA for assessment of bone mineral density and body composition.
- Administer the SF-36; the EQ-5D-5L; the MAF; the MOS-12; the PGWBI; the BPRS; the C-SSRS (Since Last Visit version)
- Administer the Hirsutism and Acne Scales (female subjects only)
- Review Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).

- Dispense study drug: first dose to be taken at home with the subject's evening meal; thereafter, study drug will be administered bid with the subject's breakfast and evening meal (doses separated by approximately 12 hours).
- Record prior and concomitant medications.
- AE monitoring.

9.7.2.1.2. Week 2 (+5 days) (at home or study site)

The following study procedures and assessments will be performed:

- Collect blood sample for hormone panel and PK.
- AE monitoring.

9.7.2.2. 8-Week Glucocorticoid Reduction Period (Week 4 to Week 12)

9.7.2.2.1. Week 4 (+5 days): Glucocorticoid Dose Reduction Step 1

Subjects will bring a urine sample that was collected at home (all voids from midnight the night before to the first morning void after awakening for the day) as specified in Section 9.3.3. Subjects should arrive at the study site prior to their morning dose of glucocorticoid and study drug. They should bring their morning dose of glucocorticoid and study drug to take at the study site after the first set of blood samples.

The following study procedures and assessments will be performed:

- Subjects will review the applicable portions of the ICF as a reminder that the glucocorticoid dose reduction will start following the Week 4 visit and about potential symptoms they may experience.
- Perform a physical examination including measurement of waist circumference.
- Perform vital signs (including weight).
- Collect blood samples for TSH and free T4; chemistry, hematology, and coagulation labs; PK; hormone panel (prior to and approximately 2 hours after morning dose of glucocorticoid and study drug).
- Collect urine sample for urinalysis; urine pregnancy test (only for female subjects of childbearing potential).
- Collect subject's at-home urine sample for urine androgen metabolites.
- Perform 12-lead ECG.
- Administer the C-SSRS (Since Last Visit version)
- Administer the Hirsutism and Acne Scales (female subjects only); and review Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).

- Review glucocorticoid dose reduction schedule, including specific instructions for Step 1 in dose reduction, possible symptoms, criteria for contacting site, and arrange time for follow-up telephone contact.
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

Study site will contact subject via telephone within 1 week following the Week 4 visit to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.2.2.2. Week 6 (+5 days) (at home or study site): Glucocorticoid Dose Reduction Step 2

The following study procedures and assessments will be performed:

- Perform vital signs including weight and orthostatics.
- Collect blood samples for chemistry labs; PK; hormone panel.
- Review glucocorticoid dose reduction schedule, including specific instructions for Step 2 in dose reduction, possible symptoms, criteria for contacting site, and arrange time for follow-up telephone contact.
- Record concomitant medications.
- AE monitoring.

If a glucocorticoid dose reduction occurred at Week 6, study site will contact subject via telephone within 1 week to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.2.2.3. Week 8 (+5 days) (telephone call visit): Telephone Contact for Glucocorticoid Dose Reduction Step 3

- If needed, study site will contact subject via telephone regarding glucocorticoid reduction. The glucocorticoid dose reduction schedule should be reviewed, including specific instructions for Step 3 in dose reduction, possible symptoms, and criteria for contacting site.
- AE monitoring.

9.7.2.2.4. Week 9 (at home or study site) (+5 days)

The following study procedures and assessments will be performed:

- Perform vital signs including weight and orthostatics.
- Collect blood sample for chemistry labs; PK; hormone panel.
- Perform a urine pregnancy test only for female subjects of childbearing potential.

- Administer the C-SSRS (Since Last Visit version).
- Review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Record concomitant medications.
- AE monitoring.

9.7.2.2.5. Week 10 (+5 days) (telephone call visit): Telephone Contact for Glucocorticoid Dose Reduction Step 4

- If needed, study site will contact subject via telephone regarding glucocorticoid reduction. The glucocorticoid dose reduction schedule should be reviewed, including specific instructions for Step 4 in dose reduction, possible symptoms, and criteria for contacting site. If a glucocorticoid dose reduction occurred at Week 10, study site will contact subject via telephone within 1 week to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.
- AE monitoring.

9.7.2.2.6. Week 12 (+5 days)

The following study procedures and assessments will be performed:

- Perform a physical examination including measurement of waist circumference.
- Perform vital signs including weight and orthostatics.
- Collect blood samples for chemistry, hematology, and coagulation labs; PK; hormone panel.
- Collect urine sample for urinalysis; urine pregnancy test (only for female subjects of childbearing potential).
- Administer the BPRS; the C-SSRS (Since Last Visit version)
- Administer the Hirsutism and Acne Scales (female subjects only); review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

Based on review of the subject's hormone levels collected up to that visit as well as based on clinical assessment, the investigator will determine the appropriate dose of glucocorticoid to continue past Week 12 (the reduced dose if tolerated, or a prior higher dose) in order to achieve adequate control of androgen levels (ie, androstenedione ≤120% of baseline or ≤upper limit of normal for age and sex).

9.7.2.3. 12-Week Glucocorticoid Optimization Period (Week 16 to Week 24)

9.7.2.3.1. Week 16 (at home or study site) (±5 days)

The following study procedures and assessments will be performed:

- Perform vital signs (including weight).
- Collect blood sample for chemistry labs; PK; hormone panel.
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Administer the C-SSRS (Since Last Visit version)
- Review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Record concomitant medications.
- AE monitoring.

9.7.2.3.2. Week 20 (±5 days) (at home or study site)

The following study procedures and assessments will be performed:

- Perform vital signs (including weight).
- Collect blood sample for chemistry labs; PK; hormone panel.
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Administer the C-SSRS (Since Last Visit version).
- Review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Record concomitant medications.
- AE monitoring.

9.7.2.3.3. Week 24 (±5 days)

Subjects will bring a urine sample that was collected at home (all voids from midnight the night before the study visit to the first morning void) as specified in Section 9.3.3. Subjects should arrive at the study site for the Week 24 visit in the morning in a fasted state (minimum 8-hour fast) and prior to their morning dose of glucocorticoid and study drug. They should bring their morning dose of glucocorticoid and study drug to take at the study site after the first set of blood samples.

The following study procedures and assessments will be performed:

- Collect blood samples for TSH and free T4; chemistry, hematology, and coagulation labs; PK; hormone panel (prior to and approximately 2 hours after morning dose of glucocorticoid and study drug); fasting metabolic panel; bone markers.
- Perform a physical examination including measurement of waist circumference.

- Perform vital signs including weight and orthostatics.
- Collect urine sample for urinalysis; urine NTx (fasting, after first morning void); urine pregnancy test only for female subjects of childbearing potential.
- Perform glucose tolerance test (only in subjects without diabetes mellitus).
- Collect subject's at-home urine sample for urine androgen metabolites.
- Perform 12-lead ECG.
- Perform testicular ultrasound (males only).
- Perform DXA for assessment of bone mineral density and body composition.
- Administer the SF-36; the EQ-5D-5L; the MAF; the MOS-12; the PGWBI; the BPRS; the C-SSRS (Since Last Visit version).
- Perform the Hirsutism and Acne Scales (female subjects only); review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

Subjects are to be advised not to change their glucocorticoid dose after Week 24 until the Month 7 visit except for sick-day guidelines (Appendix B).

9.7.3. Open-Label Treatment Period (After Week 24 up to Month 12)

9.7.3.1. 1-Month Glucocorticoid Stable Period (After Week 24 up to Month 7)

9.7.3.1.1. Telephone Contact

Sites should contact the subject within 2 weeks after the Week 24 visit to assess whether the subject has any adverse events or concerns after initiating open-label treatment.

9.7.3.2. 3-Month Glucocorticoid Reduction Period (Month 7 up to Month 10)

Subjects who were unsuccessful at achieving a reduced glucocorticoid dose with androstenedione control during the placebo-controlled period and/or who are still at a glucocorticoid dose >11 mg/m^2/day (hydrocortisone equivalents) by Month 7 should attempt to reduce their glucocorticoid dose again after completing the first month (glucocorticoid stable period) of open-label treatment (with the goal to achieve a target physiologic dose of 8 to 10 mg/m^2/day by Month 10), unless the investigator deems further attempts at dose reduction to not be advisable for that subject.

9.7.3.2.1. Month 7 (at home or study site) (±5 days)

The following study procedures and assessments will be performed:

- Perform vital signs (including weight).
- Collect blood sample for hematology and coagulation; PK; hormone panel.
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Administer the C-SSRS (Since Last Visit version)
- Review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Advise subject on glucocorticoid dose reduction as indicated.
- Record concomitant medications.
- AE monitoring.

Study site should contact subject via telephone within 1 week following the Month 7 visit to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.3.2.2. Month 8 (±5 days)

The following study procedures and assessments will be performed:

- Perform a physical examination including measurement of waist circumference.
- Perform vital signs including weight and orthostatics.
- Collect blood sample for chemistry, hematology and coagulation labs; PK; hormone levels.
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect urine sample for urinalysis.
- Perform 12-lead ECG.
- Administer the C-SSRS (Since Last Visit version).
- Administer the Hirsutism and Acne Scales (female subjects only); review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Advise subject on glucocorticoid dose reduction as indicated.
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

If a glucocorticoid dose reduction occurred at Month 8, study site should contact subject via telephone within 1 week to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.3.2.3. Month 9 (at home or study site) (±5 days)

The following study procedures and assessments will be performed:

- Perform vital signs including weight and orthostatics.
- Collect blood sample for chemistry labs; PK; hormone panel.
- Urine pregnancy test only for female subjects of childbearing potential.
- Administer the C-SSRS (Since Last Visit version).
- Review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Advise subject on glucocorticoid dose reduction as indicated.
- Record concomitant medications.
- AE monitoring.

If a glucocorticoid dose reduction occurred at Month 9, study site should contact subject via telephone within 1 week to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.3.3. 2-Month Glucocorticoid Maintenance Period (Month 10 up to Month 12)

9.7.3.3.1. Month 10 (at home or study site) (±5 days)

The following study procedures and assessments will be performed:

- Perform vital signs including weight and orthostatics.
- Collect blood sample for chemistry labs; PK; hormone panel.
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Administer the C-SSRS (Since Last Visit version).
- Review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

9.7.4. Open-Label or Double-Blind Active-Controlled Treatment Period (Month 12 to Month 18)

9.7.4.1. Month 12 (±7 days)

Subjects will bring a urine sample that was collected at home (all voids from midnight the night before to the first morning void after awakening for the day) as specified in Section 9.3.3. Subjects should arrive at the study site for the Month 12 visit in the morning in a fasted state (minimum 8-hour fast) and prior to their morning dose of glucocorticoid and study drug. They should bring their morning dose of glucocorticoid and study drug to take at the study site after the first set of blood samples.

The following study procedures and assessments will be performed:

- Perform a physical examination including measurement of waist circumference.
- Perform vital signs (including weight).
- Collect blood samples for TSH and free T4; chemistry, hematology, and coagulation labs; PK; hormone panel (prior to and approximately 2 hours after morning dose of glucocorticoid); fasting metabolic panel; bone markers.
- Perform glucose tolerance test (only in subjects without diabetes mellitus).
- Collect urine sample for urinalysis; urine NTx (fasting, after first morning void); urine pregnancy test (only for female subjects of childbearing potential).
- Collect subject's at-home urine sample.
- Perform 12-lead ECG.
- Perform testicular ultrasound (males only).
- Perform DXA for assessment of bone mineral density and body composition.
- Administer the SF-36; the EQ-5D-5L; the MAF; the MOS-12; the PGWBI; the BPRS; the C-SSRS (Since Last Visit version).
- Administer the Hirsutism and Acne Scales (female subjects only); review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

9.7.4.2. Month 13 (only for subjects re-randomized at Month 12) (±7 days)

Subjects will bring a urine sample that was collected at home (all voids from midnight the night before to the first morning void after awakening for the day) as specified in Section 9.3.3. Subjects should arrive at the study site for the Month 13 visit prior to their morning dose of

glucocorticoid and study drug. They should bring their morning dose of glucocorticoid and study drug to take at the study site after the first set of blood samples.

The following study procedures and assessments will be performed:

- Perform vital signs (including weight).
- Collect blood samples for hematology, and coagulation labs; PK; hormone panel.
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Collect subject's at-home urine sample.
- Administer the Hirsutism and Acne Scales (female subjects only); review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Perform 12-lead ECG.
- Advise subject on glucocorticoid dose reduction as indicated.
- Record concomitant medications.
- AE monitoring.

Study site should contact subject via telephone within 1 week following the Month 13 visit to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.4.3. Month 14 (at home or study site) (±7 days)

The following study procedures and assessments will be performed:

- Perform orthostatics (only for re-randomized subjects).
- Perform vital signs (including weight).
- Collect blood sample for chemistry, hematology, and coagulation labs; PK; hormone panel.
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Administer the C-SSRS (Since Last Visit version).
- Review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Advise subject on glucocorticoid dose reduction as indicated (only for re-randomized subjects).
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

For subjects who are re-randomized, if a glucocorticoid dose reduction occurred at Month 14, study site should contact subject via telephone within 1 week to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.4.4. Month 16 (at home or study site) (±7 days)

The following study procedures and assessments will be performed:

- Perform orthostatics (only for re-randomized subjects).
- Perform vital signs (including weight).
- Collect blood sample for chemistry, hematology, and coagulation labs; PK; hormone panel.
- Perform a urine pregnancy test only for female subjects of childbearing potential.
- Administer the C-SSRS (Since Last Visit version).
- Review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Advise subject on glucocorticoid dose reduction as indicated (only for re-randomized subjects).
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

For subjects who are re-randomized, if a glucocorticoid dose reduction occurred at Month 16, study site should contact subject via telephone within 1 week to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.4.5. Month 18 (±7 days)/Early Termination for subjects who discontinue prior to Month 18

Subjects will bring a urine sample that was collected at home (all voids from midnight the night before the study visit to the first morning void after awakening for the day) as specified in Section 9.3.3. Subjects should arrive at the study site for the Month 18 visit in the morning in a fasted state (minimum 8-hour fast) and prior to their morning dose of glucocorticoid and study drug. They should bring their morning dose of glucocorticoid and study drug to take at the study site after the first set of blood samples.

The following study procedures and assessments will be performed:

- Perform a physical examination including measurement of waist circumference.
- Perform vital signs (including weight).

- Collect blood samples for TSH and free T4; chemistry, hematology, and coagulation labs; PK; hormone panel (prior to and approximately 2 hours after morning dose of glucocorticoid); fasting metabolic panel; bone markers.
- Collect urine sample for urinalysis; urine NTx (fasting, after first morning void); urine pregnancy test only for female subjects of childbearing potential.
- Collect subject's at-home urine sample for urine androgen metabolites.
- Perform 12-lead ECG.
- Perform testicular ultrasound (males only).
- Perform DXA for assessment of bone mineral density and body composition (not required during an early termination visit if the subject had a DXA within 3 months prior).
- Administer the SF-36; the EQ-5D-5L; the MAF; the MOS-12; the PGWBI; the BPRS; the C-SSRS (Since Last Visit version).
- Administer the Hirsutism and Acne Scales (female subjects only); review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

9.7.5. Open-Label Extension Treatment Period (At and After Month 18)

9.7.5.1. Month 18 (±7 days)

At the Month 18 visit, if subject will be continuing into the OLE, perform the study procedures listed in Section 9.7.4.5 and the following:

- Review applicable portions of the informed consent form and confirm participation in the optional OLE.
- Dispense study drug.
- Advise subject on glucocorticoid or crinecerfont dose adjustment as indicated (following receipt of hormone panel results; Appendix C, Open-Label Extension Treatment Period Glucocorticoid and Crinecerfont Dose Adjustment Guidance).

If a glucocorticoid dose reduction occurred, study site should contact subject via telephone within 1 week to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.5.2. Open-Label Extension Month 21 (at home or study site) (±14 days)

The following study procedures and assessments will be performed:

- Perform vital signs including weight.
- Collect blood sample for chemistry and hormone panel.
- Administer the C-SSRS (Since Last Visit version).
- Review the Menstrual Cycle Questionnaire (only in subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Dispense study drug
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.
- Advise subject on glucocorticoid or crinecerfont dose adjustment as indicated (following receipt of hormone panel results; Appendix C, Open-Label Extension Treatment Period Glucocorticoid and Crinecerfont Dose Adjustment Guidance).

If a glucocorticoid dose reduction occurred, study site should contact subject via telephone within 1 week to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.5.3. Open-Label Extension Month 24 and every 12 months thereafter (±14 days)

Subjects should arrive at the study site in the morning in a fasted state (minimum 8-hour fast) and prior to their morning dose of glucocorticoid and study drug. They should bring their morning dose of glucocorticoid (if applicable) and study drug (if applicable) to take at the study site after the first set of blood samples.

The following study procedures and assessments will be performed:

- Perform a physical examination including measurement of waist circumference.
- Perform vital signs including weight.
- Collect blood samples for chemistry, hematology, and coagulation labs; hormone panel (prior to and approximately 2 hours after morning dose of glucocorticoid); and fasting metabolic panel.
- Perform glucose tolerance test (only in subjects without diabetes mellitus).
- Collect urine sample for urinalysis; urine pregnancy test only for subjects of childbearing potential.
- Perform testicular ultrasound (subjects with testes only).
- Perform DXA for assessment of bone mineral density and body composition.

- Administer the SF-36; the EQ-5D-5L; the MAF; the BPRS; and the C-SSRS (Since Last Visit version).
- Administer the Hirsutism and Acne Scales (female subjects only); review the Menstrual Cycle Questionnaire (only in subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Dispense study drug
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.
- Advise subject on glucocorticoid or crinecerfont dose adjustment as indicated (following receipt of hormone panel results; Appendix C Open-Label Extension Treatment Period Glucocorticoid and Crinecerfont Dose Adjustment Guidance).

If a glucocorticoid dose reduction occurred, study site should contact subject via telephone within 1 week to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.5.4. Open-Label Extension Month 30 and every 12 months thereafter (±14 days)

The following study procedures and assessments will be performed:

- Perform a physical examination including measurement of waist circumference.
- Perform vital signs including weight.
- Collect blood samples for chemistry, hematology, and coagulation labs; and hormone panel.
- Collect urine sample for urinalysis; urine pregnancy test only for subjects of childbearing potential.
- Administer the C-SSRS (Since Last Visit version).
- Administer the Hirsutism and Acne Scales (female subjects only); review the Menstrual Cycle Questionnaire (only in subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Dispense study drug
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.
- Advise subject on glucocorticoid or crinecerfont dose adjustment as indicated (following receipt of hormone panel results; Appendix C, Open-Label Extension Treatment Period Glucocorticoid and Crinecerfont Dose Adjustment Guidance).

If a glucocorticoid dose reduction occurred, study site should contact subject via telephone within 1 week to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.7.5.5. Open-Label Extension Early Termination

The following study procedures and assessments will be performed:

- Perform a physical examination including measurement of waist circumference.
- Perform vital signs including weight.
- Collect blood samples for chemistry, hematology, and coagulation labs; and hormone panel.
- Collect urine sample for urinalysis; urine pregnancy test only for subjects of childbearing potential.
- Perform testicular ultrasound (subjects with testes only) (not required during an early termination visit if the subject had a testicular ultrasound within 3 months prior).
- Perform DXA for assessment of bone mineral density and body composition (not required during an early termination visit if the subject had a DXA within 3 months prior).
- Administer the SF-36; the EQ-5D-5L; the MAF; the BPRS; and the C-SSRS (Since Last Visit version).
- Administer the Hirsutism and Acne Scales (female subjects only); review the Menstrual Cycle Questionnaire (only in subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

9.7.6. Follow-Up Period

9.7.6.1. Final Study Visit (28 days after last dose of study drug)

This visit is not required if the last dose of study drug was at least 28 days prior to the ET visit, or if the subject transitions during the OLE to taking commercially-available crinecerfont or to another crinecerfont study.

The following study procedures and assessments will be performed. For subjects who do not enter the OLE, the visit window is +7 days; for those who enter the OLE, the visit window is +14 days:

- Perform a physical examination including measurement of waist circumference.
- Perform vital signs (including weight).

- Collect blood sample for chemistry, hematology, and coagulation labs; hormone panel; and PK (PK not required for subjects who enter the OLE).
- Collect urine sample for urinalysis; urine pregnancy test only for female subjects of childbearing potential.
- Perform 12-lead ECG (ECG not required for subjects who enter the OLE).
- Administer the BPRS and the C-SSRS (Since Last Visit version).
- Administer the Hirsutism and Acne Scales (female subjects only); review the Menstrual Cycle Questionnaire (only in female subjects of childbearing potential who are not on hormonal or intrauterine device contraceptives).
- Record concomitant medications.
- AE monitoring.

9.8. Study Duration

The expected duration of study participation for each subject is approximately 20 months, plus a variable amount of time in the OLE (estimated average of approximately 24 months), including 1 month for screening, 6 months of blinded placebo-controlled treatment, 6 months of open-label treatment, 6 months of open-label or blinded active-controlled treatment, a variable amount of time of open-label extension period treatment, and 1 month of follow up.

The end of the study is defined as the date of the last visit shown in the Schedule of Assessments for the last subject in the study globally.

9.9. Prohibitions and Restrictions

9.9.1. Prior and Concomitant Medications

All prescription and over-the-counter medications, including dietary and herbal supplements, taken by subjects during the 30 days before screening and during the study will be entered on the Prior and Concomitant Medications eCRF.

Prohibited Medications

The following medications are prohibited from 30 days before screening until the final study visit (or early termination):

- Orally administered glucocorticoids for indications other than CAH.
- Strong inducers of CYP3A4 or CYP2B6 except topically administered medications.
- Medications that affect cortisol or glucocorticoid metabolism (eg, phenytoin, mitotane, phenobarbital, strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, cholestyramine, certain antivirals) except topically administered medications.
- Aromatase inhibitors (eg, anastrozole, letrozole, testolactone).

Corticosteroids

During the screening period, subjects should continue to maintain their glucocorticoid and (if applicable) mineralocorticoid regimen stable unless sick-day guidelines apply (Appendix B). The importance of adherence to their glucocorticoid and mineralocorticoid regimen should be stressed at the first screening visit.

The concomitant administration of certain medications with glucocorticoids can increase the risk of certain adverse effects, including hypokalemic drugs (eg, certain diuretics, amphotericin B), which can increase risk of hypokalemia, and aspirin and salicylates, which can increase risk of gastrointestinal side effects. Subjects who are on any of these medications for treatment of medical history conditions should be on a stable dose for at least 1 month prior to screening. Use of these medications as well as administration of live vaccines during the study should be avoided to the extent possible.

Subjects who are taking fludrocortisone should maintain their fludrocortisone dose stable to the extent possible, especially during the first 10 months of the study. Increases in PRA suggestive of insufficient mineralocorticoid replacement should be managed by first ensuring adequate salt intake before adjusting fludrocortisone dose. Any planned changes to the fludrocortisone dose should be discussed with the Medical Monitor and any actual changes should be documented.

Anti-androgens

Subjects who are on an anti-androgen (eg, cyproterone acetate, drospirenone, spironolactone) must be on a stable dose for at least 3 months prior to screening and should maintain a stable dose during the study to the extent possible.

Contraception Methods

Subjects of childbearing potential with fertile male partners must agree to use contraception consistently from screening until the final study visit or 30 days after the last dose of study drug, whichever is longer. Subjects with testes are not required to use contraception for the study. Acceptable methods of contraception include the following:

- Condom with or without spermicide (cream, spray, foam, gel, suppository, or polymer film)
- Diaphragm with spermicide (with or without condom)
- Cervical cap with spermicide (with or without condom)
- Vaginal sponge impregnated with spermicide (with or without condom)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal, at least 2 months prior to screening
- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted, at least 2 months prior to screening
- Bilateral tubal ligation

- Total abstinence from sexual intercourse with male partners (periodic abstinence is not acceptable)
- Sexual partner(s) who had been vasectomized at least 3 months prior to screening or medically confirmed successful procedure
- Progesterone only, where inhibition of ovulation is not the primary mode of action

9.9.2. Dietary and Other Restrictions

Subjects must arrive at the study site in a fasted state (minimum 8-hour fast) in the morning of visits on Day 1 (baseline), Week 24, Month 12, Month 24, and every 12 months thereafter to assess metabolic parameters (eg, lipids, glucose, insulin levels). Subjects should not have anything to eat during the overnight fast, but are encouraged to drink water (to avoid a hypovolemic state) and should take their usual concomitant medications (unless holding their morning glucocorticoid dose to take at the study site).

Subjects will hold their morning dose of glucocorticoids (if applicable) and the morning dose of study drug (if applicable) until after the first blood sample is obtained at the study site on visits on Day 1 (baseline), Weeks 4 and 24, and Months 12, 13 (for subjects re-randomized at Month 12), 18, 24, and every 12 months thereafter. Study drug (except at Day 1, and after Month 24 if the subject is not receiving a morning dose of crinecerfont) and glucocorticoid (unless not on a morning glucocorticoid) will be taken at the study site with a glucose load (only in subjects without diabetes mellitus; subjects with diabetes mellitus will take study drug with food) at the Day 1, Week 24, and Month 12 and 24 visits (and every 12 months thereafter), and with food at the Week 4 and the Month 13 (for subjects re-randomized at Month 12) and 18 visits.

Subjects should refrain from taking any calcium supplements for 24 hours before the DXA scans. In addition, subjects who have had procedures using contrast agents (eg, iodine, barium or nuclear medicine isotope) within 7 days before a scheduled DXA scan will be scanned after the contrast agent has cleared (approximately 7 days after administration). Subjects should be asked to remove any jewelry or dense objects from their body (watch, jewelry, underwire garments) and change into lightweight clothing without dense buttons, zippers, elastic or other materials that can interfere with the DXA measurements. Medical-type scrubs can be used for this purpose at the site's discretion.

Strenuous activity beyond what is customary for the subject should be avoided within 1 week prior to study visits.

Subjects must not donate blood or blood products within 8 weeks before Day 1 (baseline) until 30 days after the final study visit (or early termination).

Participation in another investigational drug study (except a crinecerfont study) is prohibited for at least 30 days after the last dose of study drug in the current study.

9.10. Discontinuation of Study Drug and Subject Withdrawal

Subjects can discontinue study drug or withdraw their consent to participate in the study at any time. The investigator must discontinue study drug dosing or withdraw any subject from the study if a subject requests study drug dosing to be discontinued or to be withdrawn from the

study, respectively. All subjects prematurely discontinuing study drug dosing prior to Month 18 should continue study participation to be followed for safety and efficacy outcomes up to the Month 18 visit; subjects who discontinue study drug dosing during the OLE will be withdrawn. Subjects who discontinue study drug prior to Month 12 are ineligible for re-randomization and the OLE.

9.10.1. Discontinuation of Study Drug Dosing

If a subject prematurely discontinues study drug dosing, the investigator will record the reason for discontinuation on the relevant eCRF. Subjects who prematurely discontinue study drug dosing prior to Month 18 will not be automatically withdrawn from the study and should continue participation in the study through Month 18. Data for any outcome measures, particularly the primary and secondary endpoints, as well as safety follow-up, are important to collect. For any subsequent study visits after study drug is prematurely discontinued, subjects should have 1 final PK sample collected (ie, subsequent PK samples are not required); however, subjects should continue with study assessments at the study site or with at-home visits through the Month 18 visit. Subjects should be followed for safety evaluations (which can be done at scheduled visits) for at least 4 weeks after the last dose of study drug. If medically indicated, treatment with medication listed under Section 9.9.1 is no longer prohibited after study drug discontinuation.

Subjects who had adjustment of their glucocorticoid dose (eg, decreased dose) after initiation of study drug may require monitoring and adjustment of their glucocorticoid dose (eg, return to original dose) when study drug is discontinued.

Reasons for discontinuation of study drug dosing are:

- Withdrawal by subject
- Death
- Lost to follow-up
- Site termination by the Sponsor
- Study termination by the Sponsor
- AE
- Pregnancy
- Lack of efficacy
- Protocol deviation
- Protocol-specified withdrawal criterion met
- Investigator decision
- Sponsor decision

The investigator must discontinue study drug dosing if the subject experiences any of the following:

- QTcF value >500 msec (cardiologist verified) on any ECG tracing.
- If the subject exhibits suicidal behavior, or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.

It is crucial to obtain follow-up data for any subject who discontinues study drug dosing because of an AE, abnormal laboratory test, vital sign measurement, physical examination, or ECG finding. In any case, every effort must be made to undertake safety follow-up procedures.

9.10.2. Withdrawal from Study

If a subject prematurely withdraws from the study (either prior to Month 18, or during the OLE), the investigator will record the reason for withdrawal on the relevant eCRF. All subjects who withdraw from the study prematurely will be asked to have all early termination assessments performed. Subjects who complete the Month 18 visit but elect not to participate in the optional OLE will be considered to have completed the initial 18-month study; this will not be considered to be a premature withdrawal.

Reasons for withdrawal from study are:

- Withdrawal by the subject
- Death
- Lost to follow-up
- Site terminated by Sponsor
- Study terminated by Sponsor
- Investigator decision
- AE
- Protocol deviation
- Sponsor decision

9.10.3. Sponsor's Termination or Suspension of Study or Study Site

The Sponsor or designee reserves the right to close a study site, terminate or suspend the entire study, or terminate or suspend the study at individual sites, at any time for any reason. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate therapy and/or follow-up.

10. STUDY DRUG

10.1. Crinecerfont

Crinecerfont will be supplied as capsules containing 50 mg of crinecerfont free base for oral administration. Subjects will administer 100 mg bid (200 mg total daily dose). Subjects with glucocorticoid dose >11 mg/m^2/day at Month 12 will be re-randomized to continue crinecerfont at 100 mg bid or adjust their crinecerfont dose to 100 mg qAM and 200 mg qPM.

Starting at Month 18, all subjects who are continuing in the OLE will initially receive open-label crinecerfont 100 mg bid. If the subject has inadequate disease control despite receiving glucocorticoid treatment at their target dose (in the opinion of the investigator), the crinecerfont dose may be increased to 100 mg qAM and 200 mg qPM (including at Month 18, after laboratory results are available). If the increased dose of 100 mg qAM and 200 mg qPM is not well tolerated, the dose may be reduced back to 100 mg bid. After the Month 24 visit, an alternative dosing regimen of once daily 200 mg qPM can be considered per the investigator (Appendix C). Crinecerfont doses should generally only be adjusted at or shortly after study visits (after laboratory results are available).

10.2. Placebo

Matching placebo capsules are identical in appearance to crinecerfont and will be orally administered as needed to maintain the blind as required per applicable study period (ie, double-blind, placebo-controlled treatment period or double-blind, active-controlled treatment period).

10.3. Study Drug Supplies

NBI or its designee will provide the study center with sufficient capsule supplies for the completion of the study. Study drug will be supplied in blister cards through Month 18, and may be supplied in either blister cards or bottles during the OLE at the discretion of the Sponsor.

If needed in order to ensure continued access to study drug (eg, in the event that a subject is not able to go to the study site when study drug is to be dispensed), study drug may be delivered from the site's pharmacy to the subject's place of residence by a distributor independent from the Sponsor. The subject's name, address, and other contact details will not be accessible to the Sponsor, and the distributor will not have access to the subject's health information.

10.4. Study Drug Packaging and Labeling

All packaging and labeling operations will be conducted according to Good Manufacturing Practice (GMP) and GCP per ICH guidelines. The study drug will be sent to designated staff at the study center, who must complete and return the Drug Supply Confirmation to NBI or its designee verifying receipt of the drug.

The study drug label will list information in accordance with applicable regulatory requirements.

10.5. Study Drug Administration

Subjects will take a study drug capsules by mouth beginning with the evening meal on Day 1, and then with breakfast and the evening meal (doses separated by approximately 12 hours) for the remainder of the treatment period. Each meal should be completed within 30 minutes of taking study drug. If the subject is on crinecerfont 200 mg qPM (eg, after the Month 24 visit), study drug will be taken with the evening meal only.

If a subject forgets or is unable to take the study drug, the subject should take his or her dose of study drug as soon as possible, as long as the subject's next dose will be at least 8 hours later. The subject will need to skip the dose if he or she is unable to take the study drug at least 8 hours prior to the next dose.

See Section 9.9.2 for restrictions regarding study drug administration.

10.6. Study Drug Storage

Crinecerfont capsules should be refrigerated (2° to 8°C [36° to 46°F]) and stored in a locked area accessible only to the pharmacist or designee until dispensing. Subjects will be instructed to store study drug refrigerated (2° to 8°C [36° to 46°F]).

Study drug should be stored and inventoried according to applicable regulations and study procedures.

10.7. Blinding

This study includes a 24-week double-blind, placebo-controlled treatment period, followed by a 6-month open-label treatment period during which all subjects will receive crinecerfont. There is an additional 6-month dose adjustment period during which subjects will either receive open-label treatment or will be re-randomized to receive double-blind, active-controlled treatment. Subjects who are re-randomized will either continue to receive crinecerfont 100 mg bid or adjust their crinecerfont dose to 100 mg qAM and 200 mg qPM. Study drug dosing will be blinded such that re-randomized subjects will be taking the same number of capsules in the morning and evening across the 2 treatment groups.

The subject, investigator, and all study center personnel will remain blinded to the subject's randomized treatment assignment(s) during the entire study. The Sponsor will be blinded until all subjects complete the Week 24 visit, at which time a limited number of Sponsor personnel will be unblinded to conduct the Week 24 final analysis. Sponsor personnel with direct contact with the study site will remain blinded to individual subject's randomized treatment assignment(s) during the entire study. Clinical trial material supply chain personnel who are not involved in decisions regarding subjects' study treatment will not be blinded.

The randomization code will be broken for an individual subject only if the subject is pregnant, experiences an SAE that the investigator feels cannot be adequately treated without knowing the identity of the subject's treatment assignment, or for regulatory reporting requirements. In the case of a medical emergency in which knowledge of the identity of the study treatment is important for subject management, the investigator has the responsibility to decide whether to break the blind; treatment assignments would be unblinded using the IRT. It is recommended

that the investigator contact the Study Medical Monitor (or designee) before unblinding if it would not result in unnecessary delay to the immediate medical management of the subject. Documentation of the unblinding must be maintained.

10.8. Study Drug Accountability

Subjects will bring all unused study drug and empty drug packaging material to the center at specified study visits for drug accountability and reconciliation by study center personnel. A dosing compliance check will be performed by counting the capsules returned at each study visit.

The designated pharmacist or qualified personnel will be responsible for maintaining accurate records of the quantity and dates of all study drug supplies received, dispensed, and returned. The quantity of study drug lost must also be accounted for and documented.

10.9. Study Drug Return

Returns will be shipped to NBI or its designee during or at the completion of the study according to instructions provided by NBI or its designee, or will be managed by an alternative disposition authorized by NBI, according to applicable state and federal regulations and study procedures.

11. ADVERSE EVENTS

All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or identified by other means, will be recorded from the time the subject has signed the ICF until the subject's final study visit (or upon early termination).

11.1. Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) subject deterioration beyond what would be expected due to the primary illness; (3) intercurrent illness; and (4) drug interaction.

All suicidal behaviors and clinically significant suicidal ideations will be documented as an AE.

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms. Following questioning and evaluation, all AEs, whether believed by the investigator to be related or unrelated to the study drug, must be documented in the subject's medical records, in accordance with the investigator's

normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the study drug.

The following are not considered AEs:

- Continuous persistent disease/symptom present before drug administration, unless it unexpectedly progresses, or increases in severity following drug administration.
- Treatment failure or lack of efficacy.
- Pregnancy
- Overdose of either study drug or concomitant medication without any clinical signs or symptoms

11.1.1. Intensity of Adverse Events

AEs must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 4, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious."

Table 4: Intensity of Adverse Events

Grade	Intensity
Mild	An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe	An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

11.1.2. Relationship to Study Drug

The investigator will document his/her opinion of the relationship of the AE to treatment with study drug using the criteria outlined in Table 5. An AE is deemed associated with the use of the study drug "if there is a reasonable possibility that the drug caused the AE" (otherwise referred to as a suspected adverse reaction). Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE (Title 21 Code of Federal Regulations [CFR] 312.32 [a]).

Table 5: Relationship of Adverse Events to Study Drug

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure.
Possible	An adverse event in which there is reasonable possibility that the drug caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event.
Unlikely	A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or suspected response pattern to the suspected drug; but that could reasonably be explained by known characteristics of the subject's clinical state.
Not Related	Any event that does not meet the above criteria.

11.2. Recording Adverse Events

For randomized subjects, each AE will be listed as a separate entry on an AE eCRF. Screen failure subjects will have AE information noted only in the source document. The investigator (or designee) will provide information on dates of onset and resolution, intensity, seriousness, frequency, action(s) taken, changes in study drug usage, relationship to study drug, and outcome.

11.3. Poststudy Follow-Up of Adverse Events

All AEs, including clinically significant changes in ECGs, physical examination findings, or isolated clinically significant laboratory findings must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up.

AEs ongoing at the final visit or at early termination will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves or until the subject is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals, as is practical.

11.4. Serious Adverse Events

All SAEs will be recorded from the time the subject has signed the ICF until the final study visit. Investigators are not obligated to actively seek SAEs after a subject has withdrawn from or completed the study. However, if the investigator learns of any SAE, including a death, at any time after a participant has been withdrawn from or has completed the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor as described in Section 11.4.3.

11.4.1. Definition of a Serious Adverse Event

An SAE is any AE that results in any of the following outcome:

- Death.
- A life-threatening AE. Life-threatening means that the subject was, in the view of the investigator or Sponsor, at immediate risk of death from the reaction as it occurred. It does not mean that hypothetically the event might have caused death if it occurred in a more serious form.
- Inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for elective treatment or a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE. Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization.
- A persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization. These events may be considered serious when, based on appropriate medical judgment, they may jeopardize the health of the subject and may require medical or surgical intervention to prevent one of the outcomes listed. Any other event thought by the investigator to be serious should also be reported, following the reporting requirements detailed in this section. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.4.2. Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized.

If an investigator becomes aware of an SAE within the time of informed consent until 30 days after the last dose of study drug or final study visit, whichever is longer in duration, then the event must be documented and reported as described in Section 11.4.3.

11.4.3. Reporting Serious Adverse Events and Pregnancies

SAEs and pregnancies must be reported within 24 hours of first knowledge of the event by study personnel to NBI Drug Safety and Pharmacovigilance (DSPV) Department. Reports of SAEs and pregnancies must be followed by a fax or email of the SAE or Pregnancy Form. It is important that the investigator provides his or her assessment of relationship to study drug at the time of the initial SAE report.

For SAEs and other immediately reportable events, contact DSPV:

DSPV facsimile: **+1 (888) 617-7551**

DSPV e-mail: **cds@neurocrine.com**

11.4.4. Expedited Safety Reports

NBI or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (as defined in Section 11.1.2) that is considered both serious and unexpected within 15 calendar days and for any unexpected fatal or life-threatening experience within 7 calendar days to the applicable regulatory authority(ies); or according to country-specific regulations.

NBI or its representatives will send copies of each safety report submitted to regulatory authorities to the investigators. The safety report must be submitted to the appropriate IRB/IEC as soon as possible. Documentation of the submission to the IRB/IEC and receipt by the IRB/IEC (if applicable) must be retained for each safety report.

11.5. Pregnancy

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in female subjects who received crinecerfont will be followed to assess for congenital anomaly. Subjects of childbearing potential must be counseled at all visits to continue using contraception (see inclusion criterion #6 in Section 8.1) until 30 days after the last dose of study drug. If at any time between the time the subject signs the ICF and the last study visit, a subject believes she is pregnant, the subject will be instructed to return to the study center within 24 hours and undergo a serum pregnancy test to confirm pregnancy. Subjects confirmed to be pregnant may be unblinded.

All confirmed pregnancies in subjects who received study drug must be immediately reported to NBI (see Section 11.4.3 for contact information), followed by fax or email of the pregnancy form to NBI DSPV. A first trimester ultrasound may be requested for all confirmed pregnancies. Pregnancies in subjects who received crinecerfont will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

12. DOCUMENTATION OF DATA

12.1. Case Report Forms

The eCRF data for this study are being collected with an electronic data capture (EDC) system (Rave®) provided by Medidata Solutions Incorporated, NY, USA. The EDC system and the

study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study specific eCRFs will be conducted by NBI and the required documentation will be maintained in the Trial Master File.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by authorized study personnel in the EDC system, with the exception of data captured in an electronic format, which will be loaded electronically into the appropriate eCRFs. All data entered into the eCRF will be supported by source documentation. The eCRF for each subject must be reviewed by the investigator and signed on the appropriate eCRF page(s). This should be done as soon as possible after the subject completes the study.

The investigator or an authorized member of the investigator's staff will make any necessary additions/corrections to the eCRF. All change information, including the date, person performing the corrections, and reason for the change will be available via the electronic audit trail, which is part of the EDC system. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by NBI (or designee). NBI will also be allowed access to all source documents and medical records pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and enter his or her electronic signature on the eCRFs as evidence thereof.

Medidata will provide access to the NBI portal of the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from study centers at the end of the center’s participation in the study. Data from the EDC system will be archived on appropriate data media and provided to the investigator at that time as a durable record of the center’s eCRF data. Although not required, the investigator may make paper printouts from that media.

All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by NBI and/or health authority representatives at any time. The Principal Investigator will agree to the inspection of study-related records by health authority representatives and/or NBI.

12.2. Data Capture, Review, and Validation

Data entered in the EDC system will be verified against the source data by NBI (or designee). Any discrepancies will be corrected on-line by authorized study center personnel. Automated (computer-generated) logic checks will run in order to identify items such as inconsistent study dates. In addition, manual review/checks may be performed by NBI on the data. Any inconsistencies/errors/omissions identified will be sent to the study center (via an electronic query) for the necessary corrections to be made to the eCRF. Once entered and saved in an eCRF, data immediately become part of the study database and are available to NBI.

12.3. Coding Dictionaries

AEs and medical history will be coded using the chosen version of the Medical Dictionary for Regulatory Activities (MedDRA), per NBI. Prior and concomitant medications will be coded using the chosen version of the World Health Organization Drug Dictionary, per NBI.

13. STATISTICAL AND ANALYTICAL PLAN

13.1. Overview

This section represents a brief description of the planned primary analysis of the primary and key secondary endpoints as well as the planned interim analysis that will occur when approximately 50% of the planned number of enrolled subjects have had the opportunity to complete the Week 24 assessments at the end of the double-blind treatment period. A comprehensive and detailed statistical analysis plan (SAP) will be generated and finalized prior to the Week 24 study database interim lock and treatment unblinding for the interim analysis. The SAP will describe all planned analyses, including sensitivity analyses of the primary and key secondary endpoints, analyses of other secondary and exploratory endpoints, and analyses of data from the open-label phase.

13.2. Primary Estimand

The primary estimator is the least-squares mean treatment difference between the crinecerfont and placebo treatment groups in the percent change from baseline in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for body surface area [BSA; mg/m^2/day]) at Week 24, while Week 24 androstenedione is adequately controlled at ≤120% of baseline or ≤ULN for age and sex, in all randomized subjects, regardless of adherence to study drug. Subjects who have a decrease in glucocorticoid daily dose at Week 24 but who are not able to control their androstenedione levels at ≤120% of baseline or ≤ULN for age and sex will be considered to have a zero percent change from baseline in the glucocorticoid daily dose at Week 24. Subjects who are missing Week 24 glucocorticoid dose data or all Week 24 androstenedione levels will have their data imputed through a multiple imputation procedure. Missing data will be imputed for subjects in the crinecerfont treatment group using retrieved data (ie, observed data from subjects who discontinued study drug) in the crinecerfont treatment group, provided there is sufficient retrieved data. Otherwise, missing data will be imputed using observed data from subjects in the placebo treatment group. For subjects in the placebo treatment group, missing data will be imputed using observed data from subjects in the placebo treatment group.

13.3. Statistical Hypotheses

The null hypothesis for the primary endpoint is that there is no difference between the crinecerfont and the placebo treatment groups in the mean percent change from baseline in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for body surface area [mg/m^2/day]) at Week 24. In other words, H_0: $\mu_1 = \mu_2$ where μ_1 is the mean percent change from baseline in glucocorticoid daily dose in the placebo group at Week 24 and μ_2 is the mean percent change from baseline in glucocorticoid daily dose in the crinecerfont treatment group at

Week 24. The alternative hypothesis is that there is a difference between the crinecerfont treatment group and the placebo group in the mean percent change from baseline in glucocorticoid daily dose at Week 24 (ie, H_1: $\mu_1 \neq \mu_2$).

13.4. Sample Size Determination

The protocol-specified sample size of 165 subjects (110 in the crinecerfont treatment group and 55 in the placebo group) is based on a power calculation for the primary endpoint and considerations for the size of the safety database. Based on a 2-sample t-test, an effect size of 0.75 with a sample size of at least 90 subjects (60 in the crinecerfont treatment group and 30 in the placebo treatment group) will have greater than 90% power to detect a treatment difference at a 0.05 level of significance. With the full sample size of 165 subjects, there is greater than 90% power to detect an effect size as small as 0.55.

To mitigate against the uncertainty of sample size assumptions, an interim analysis is planned to evaluate the study to stop early for futility, increase the sample size, or continue the study as planned. The decision to increase the sample size will be based on the conditional power calculated at the interim analysis and could result in an increase of the planned sample size up to a maximum of 210 subjects (see Section 13.7).

13.5. Analysis Sets

The analysis sets to be used for the analyses described in this protocol are defined in Table 6. Additional analysis sets may be specified in the SAP.

Table 6: Analysis Sets

Analysis Sets	Description
Full Analysis Set	The full analysis set (FAS) includes all randomized subjects. Subjects will be analyzed according to their randomized treatment group, regardless of adherence to study drug administration.
Re-randomization Analysis Set	The re-randomization analysis set (RAS) includes all subjects who are re-randomized at Month 12. Subjects will be analyzed according to their Month 12 randomized treatment group, regardless of adherence to study drug administration.
Safety Analysis Set	The safety analysis set (SAS) will include all randomized subjects who take at least 1 dose of study drug and have any postbaseline safety data during the double-blind placebo-controlled period. Subjects will be analyzed according to their randomized treatment group, unless they receive the incorrect study drug for the entire double-blind treatment duration.

13.6. Statistical Analyses

Descriptive and inferential statistical methods will be used to evaluate and summarize the data from this study. Descriptive statistics typically refers to the number of subjects (n), mean, SD or SE, median, first (Q1) and third (Q3) quartile, minimum, maximum, and confidence intervals for continuous variables; and refers to the number and percentage of subjects for categorical variables. Inferential statistics refers to the analysis results from hypothesis tests, which will be

performed to assess differences between treatment groups (crinecerfont and placebo). The 2-sided level of significance used in this study is 0.05.

13.6.1. Efficacy Analyses

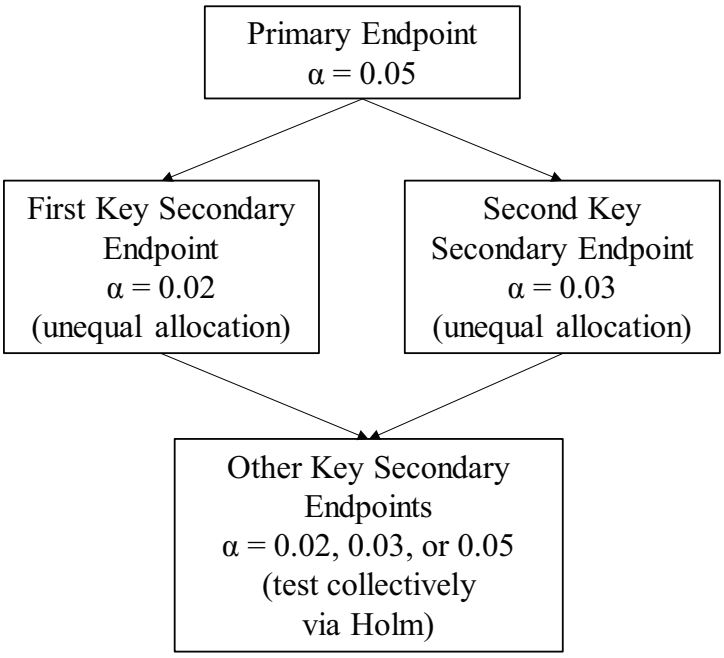
This section is a summary of the planned statistical methods for the primary analysis of the primary and key secondary endpoints, as well as the planned interim analysis of the primary endpoint. Additional analysis details will be described in the SAP.

13.6.1.1. Procedure to control for multiple comparisons

The testing procedure described below will be used to control the familywise Type I error rate for the primary and key secondary endpoints at the final analysis (Figure 4). This study will use a significance level of 0.05 in the final analysis. All significance levels noted below are 2-sided. All other p-values will not be adjusted for multiplicity and should be considered as nominal p-values.

- The primary endpoint will be tested using a significance level of 0.05.
- If the primary endpoint is statistically significant, then the first 2 key secondary endpoints will be tested using an unequal allocation of significance levels. The change from baseline at Week 4 in androstenedione will be tested using a significance level of 0.02. The achievement of a reduction in glucocorticoid daily dose to physiologic levels ($\leq$11 mg/m^2/day hydrocortisone equivalents adjusted for BSA) will be tested using a significance level of 0.03.
- The family of remaining key secondary endpoints will be tested using the Holm procedure (Holm, 1979). The significance level for this family of endpoints will be dependent on whether the first 2 key secondary endpoints are statistically significant (Wiens, 2003). If both are statistically significant, then the significance level for this family of endpoints will be 0.05. If only one is statistically significant, then the significance level for that endpoint will be used for this family of endpoints. If neither is significant, then this family of endpoints will not be tested for statistical significance. However, nominal p-values will be produced.

Figure 4: Procedure to Control for Multiple Comparisons



13.6.1.2. Primary endpoint

The primary endpoint is the percent change from baseline in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for BSA [mg/m^2/day]) at Week 24, while Week 24 androstenedione is adequately controlled at ≤120% of baseline or ≤ULN for age and sex. Baseline androstenedione will be defined as the Day 1 post-morning glucocorticoid dose androstenedione value. If this value is missing, the last post-morning glucocorticoid dose androstenedione value prior to Day 1 will serve as the baseline. The post-morning glucocorticoid dose androstenedione value at Week 24 will be used for the comparison to the baseline androstenedione in assessing control (as defined above). If a subject is missing their Week 24 post-glucocorticoid dose androstenedione value then the pre-glucocorticoid dose androstenedione values at Day 1 (baseline) and Week 24 will be used instead.

Subjects who have a decrease in glucocorticoid daily dose at Week 24 but who are not able to control their androstenedione levels at ≤120% of baseline or ≤ULN for age and sex will be considered to have a zero percent change from baseline in the glucocorticoid daily dose at Week 24. Subjects who are missing Week 24 glucocorticoid dose data or all Week 24 androstenedione levels will have their data imputed through a multiple imputation procedure. Missing data will be imputed for subjects in the crinecerfont treatment group using retrieved data (ie, observed data from subjects who discontinued study drug) in the crinecerfont treatment group, provided there is sufficient retrieved data. Otherwise, missing data will be imputed using observed data from subjects in the placebo treatment group. For subjects in the placebo treatment group, missing data will be imputed using observed data from subjects in the placebo treatment group.

Because the total sample size could potentially be increased in a data dependent manner based on the interim analysis results, the final analysis of these data will not use the conventional statistic to determine if statistical significance is reached. Instead, it will use the weighted statistic

proposed by Cui, Hung, and Wang (1999) (referred to as the "CHW approach") and independently by Lehmacher and Wassmer (1999) in which the independent increments of the Z statistics (ie, the Wald statistics constructed using model-based treatment effect estimates) of the 2 stages are combined by prespecified weights that are based on the planned proportion of total number of subjects at which the interim analysis would be taken if there were no change in the design. As such, the primary analysis of the primary endpoint will be comprised of test statistics from stage 1 of the study (the interim dataset) and stage 2 of the study (final data set excluding subjects analyzed in the interim dataset). Each test statistic will be generated using an analysis of covariance (ANCOVA) model applied to the 2 independent datasets. The model will include treatment group, baseline glucocorticoid daily dose, and stratification factors used in the randomization. This analysis will be performed using the full analysis set (FAS).

13.6.1.3. Key secondary endpoints

The first key secondary endpoint is the change from baseline in serum androstenedione at Week 4. The pre-morning glucocorticoid dose androstenedione values at Day 1 (baseline) and Week 4 will be used in the calculation of this endpoint. If a subject is missing their Week 4 pre-glucocorticoid dose androstenedione value then the post-glucocorticoid androstenedione values at Day 1 (baseline) and Week 4 will be used instead. The primary analysis of this endpoint will be performed using an ANCOVA model. The model will include treatment group, baseline serum androstenedione, and stratification factors used in the randomization. Subjects who are missing all androstenedione levels at Week 4 will have their data imputed through a multiple imputation procedure. Missing data will be imputed for subjects in the crinecerfont treatment group using retrieved data (ie, observed data from subjects who discontinued study) in the crinecerfont treatment group, provided there is sufficient retrieved data. Otherwise, missing data will be imputed using observed data from subjects in the placebo treatment group. For subjects in the placebo treatment group, missing data will be imputed using observed data from subjects in the placebo treatment group. This analysis will be performed using the FAS.

The second key secondary endpoint is the achievement of a reduction in glucocorticoid daily dose to physiologic levels (≤11 mg/m^2/day hydrocortisone equivalents adjusted for BSA) at Week 24, while Week 24 androstenedione is adequately controlled at ≤120% of baseline or ≤ULN for age and sex. Androstenedione levels used to assess adequate control is as described for the primary endpoint above. The primary analysis of this endpoint will be performed using a Cochran-Mantel-Haenszel (CMH) test. The CMH test will compare treatment groups and will include the stratification factors used in the randomization. Subjects whose androstenedione levels at Week 24 are not controlled will be considered non-responders. Subjects who are missing their glucocorticoid dose or all androstenedione data at Week 24 will have their data imputed through a multiple imputation procedure. Missing data will be imputed for subjects in the crinecerfont treatment group using retrieved data (ie, observed data from subjects who discontinued study drug) in the crinecerfont treatment group, provided there is sufficient retrieved data. Otherwise, missing data will be imputed using observed data from subjects in the placebo treatment group. For subjects in the placebo treatment group, missing data will be imputed using observed data from subjects in the placebo treatment group. This analysis will be performed using the FAS.

Additional key secondary endpoints are the changes from baseline in HOMA-IR, weight, and fat mass at Week 24, which will be analyzed using an ANCOVA model. The model will include treatment group, corresponding baseline values, and stratification factors used in the randomization. Subjects who are missing data at Week 24 will have their data imputed through a multiple imputation procedure using the retrieved data method as described for the first key secondary endpoints above. This analysis will be performed using the FAS.

13.6.1.4. Secondary endpoints

Secondary endpoints will be compared by treatment group and will not be adjusted for multiplicity. Analysis methods for these endpoints will be described in the SAP. These analyses will be performed using observed data in the FAS. The secondary endpoints include change from baseline to Week 4 for 17-OHP and changes from baseline to Week 24 in:

- Blood pressure
- Glucose tolerance (subjects without diabetes mellitus)
- Waist circumference
- Menstrual regularity (women not using hormonal or IUD contraception only)
- TART size and characteristics (men only)

An additional secondary endpoint is the percent change from Month 12 in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for BSA [mg/m^2/day]) at Month 18, while Month 18 androstenedione is adequately controlled at ≤120% of baseline or ≤ULN for age and sex. This additional secondary endpoint will be compared by treatment group randomly assigned at Month 12 and will not be adjusted for multiplicity. Analysis methods for this endpoint will be described in the SAP. This analysis will be performed using observed data and restricted to subjects with a glucocorticoid daily dose (in hydrocortisone equivalents adjusted for BSA [mg/m^2/day]) >14 mg/m^2/day at Month 12 in the RAS.

13.6.2. Safety Analyses

Safety data from the double-blind, placebo-controlled period through Week 24, the open-label period through Month 12, the double-blind, active-controlled period through Month 18 for those subjects who were re-randomized, and the open-label extension treatment period from Month 18 onwards will be analyzed separately. The subject incidence of treatment-emergent adverse events will be tabulated by randomized treatment group assignment at baseline or at Month 12, as appropriate, for adverse events, serious adverse events, fatal adverse events, and adverse events leading to discontinuation of study drug. Descriptive statistics by randomized treatment group assignment at baseline or at Month 12, as appropriate, will be generated for additional safety data, including selected laboratory analytes, vital signs, ECG parameters, C-SSRS, and BPRS. The safety analyses described above will also be generated for safety data collected during the open-label extension period by crinecerfont dose level and all subjects combined.

13.7. Week 24 Interim Analysis

An unblinded interim analysis on the primary endpoint using the "promising zone" method (Mehta and Pocock, 2011) will be conducted when approximately the first 83 subjects (approximately 50% of the planned number of enrolled subjects) have had the opportunity to complete the Week 24 assessments. The primary endpoint will be analyzed in a similar fashion at the interim analysis and at the final analysis using an ANCOVA model as described in Section 13.6.1.2. The interim analysis will be conducted by an independent statistical center (ISC) and will be evaluated by the DMC. The DMC will assess futility and consider sample size re-estimation based on the observed treatment effect and the conditional power at the time of the interim analysis. Conditional power is the probability that, conditional on the current value of the test statistic at the interim analysis, the study will achieve statistical significance at the final analysis. The adaptive elements of this interim analysis and the criterion for each DMC recommendation are detailed in an Adaptation Plan. Access to the Adaptation Plan will be limited to the ISC, DMC, and selected Sponsor staff assigned to the crinecerfont program, specifically the biostatisticians, regulatory lead, and program team lead.

Based on the interim analysis results, one of the following recommendations will be made by the DMC:

- Stop the study for futility
- Continue the study to the planned sample size
- Increase the sample size to a maximum of 210 subjects

The DMC will communicate the recommendation, without disclosing the numerical results, to a very limited number of Sponsor personnel or their designees who are not directly involved with the conduct or oversight of the study and will include a biostatistician and a clinician.

13.8. Week 24 Final Analysis

The final unblinded analysis of the double-blind, placebo-controlled period will be conducted once all subjects have completed the Week 24 visit. Data through Week 24, including the primary, key secondary, and secondary endpoints, will be analyzed. Since this analysis includes all data for the primary and key secondary endpoints, there will be no adjustments to the level of significance and the full 0.05 level of significance will be used. Following this analysis, the subject, investigator, all study center personnel, and Sponsor personnel with direct contact with the site will continue to be blinded to the subject's blinded treatment assignment (Section 10.7).

13.9. Month 12 and Month 18 Final Analyses

The final analysis of the open-label period will be conducted once all subjects have completed their Month 12 visit. At this time, all data collected from Week 24 up to Month 12 will be analyzed.

The final unblinded analysis of the open-label or double-blind, active-controlled period will be conducted once all subjects have completed the Month 18 visit. Data from Month 12 through Month 18, including the secondary endpoint described in Section 13.6.1.4, will be analyzed. Following this analysis, the subject, investigator, all study center personnel, and Sponsor

personnel with direct contact with the site will continue to be blinded to the subject's blinded treatment assignment.

14. REGULATORY AND ETHICAL ISSUES

14.1. General Legal References

The study will be carried out according to provisions of the US CFR, the US Food and Drug Administration (FDA), the laws and regulations of the country in which the study is conducted, and the ICH Guidelines for GCP. All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by the Sponsor or its representative, health authority, or IRB/IEC representatives at any time. The investigator must agree to the inspection of study related records by health authority representatives and/or the Sponsor or its designee.

14.2. Institutional Review Board/Independent Ethics Committee

The final approved protocol and the ICF will be reviewed by the IRB/IEC at the study center. The committee's decision concerning conduct of the study will be sent in writing to the investigator and a copy will be forwarded to the Sponsor. The investigator must agree to make any required progress reports to the IRB/IEC, as well as reports of SAEs, life-threatening problems, or death.

A list of members participating in the IEC/IRB meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the site study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

14.3. Protocol Adherence – Amendments

The protocol must be read thoroughly, and the instructions must be followed exactly. Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator and the Sponsor. The IRB/IEC and local health authorities will be notified of all amendments to the protocol in accordance with local regulations.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator and/or sponsor/CRO to the IEC/IRB and to the national competent (health) authority in accordance with local procedures and regulations.

14.4. Required Documents

The investigator must provide NBI or its designee with the following documents before the enrollment of any subject (originals should be kept by the investigator in the investigator's study regulatory document binder):

- Signed copy of the protocol signature page.
- Investigator's Brochure acknowledgement page.
- Completed and signed statement of investigator qualifications, as applicable.
- Financial disclosure documentation as required.
- Curriculum vitae and current medical license of the investigator and subinvestigators.
- Letter of approval from the IRB/IEC for protocol and consent form.
- Copy of the IRB/IEC approved written ICF to be used.
- Laboratory documents (certifications/accreditations, normal ranges) if not provided by a central laboratory.

14.5. Informed Consent

Prior to any study-related procedures, subjects must provide written informed consent (which may be done remotely, if allowed and remote consenting procedures are in place), as required by the governing IRB/IEC and according to local laws and regulations. Prior to any OLE-related study procedures, subjects will review applicable portions of the informed consent form and confirm whether they will participate in the optional OLE.

Each subject's chart will include the signed ICF for study participation. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the study.

14.6. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and may periodically request review of the investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The investigator or appointed delegate will receive the study monitor during these on-site visits, will cooperate in providing the documents for inspection, and will respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

14.7. Quality Assurance

The study will be conducted in accordance with NBI's standard operating procedures designed to ensure that all procedures are in compliance with GCP and FDA Guidelines, and according to national law. Quality assurance audits may be performed at the discretion of NBI.

14.8. Record Retention

Study records should be retained in compliance with the federal regulations of the clinical site.

NBI may request these records to be retained for a longer period if required by applicable regulatory requirements or sponsor contractual obligations. If the investigator is unable to retain the study documents for the required amount of time, NBI must be informed of the individual who will be assuming this responsibility.

14.9. Confidentiality

NBI or its designee, and the study center affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be identified only by an identification number.

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of NBI; it shall not be disclosed to others without written consent of NBI; and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may be disclosed and/or used only by NBI as deemed necessary. To allow the use of the information derived from this clinical study and to ensure compliance to current federal regulations, the investigator is obliged to furnish NBI with the complete test results and all data compiled in this study.

15. STUDY COMMENCEMENT AND DISCONTINUATION

Upon satisfactory receipt of all required regulatory documents, NBI (or designee) will arrange that all study materials be delivered to the study site. Subject enrollment should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo orientation to include review of the study protocol, instructions for eCRF completion, AE reporting, and overall responsibilities including those for drug accountability and study file maintenance.

If the study is discontinued, all subjects should undergo a complete follow-up examination. Any clinically relevant finding, including laboratory values of potential clinical concern, and adverse experiences will be followed until they resolve or return to a clinically acceptable level.

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APPENDIX A. HYDROCORTISONE DOSE EQUIVALENT CONVERSION TABLE

Glucocorticoid	Hydrocortisone dose equivalent conversion
Methylprednisolone	4×
Prednisolone	4×
Prednisone	4×
Dexamethasone	60×

Auchus and Arlt, 2013; Speiser et al., 2018.

APPENDIX B. SICK-DAY GLUCOCORTICOID DOSING GUIDELINES

Type of Illness	Instruction
Minor illness or low-grade fever	Take hydrocortisone 10 mg three times a day in addition to usual glucocorticoid regimen.
Major illness or high-grade fever	Take hydrocortisone 20 mg three times a day in addition to usual glucocorticoid regimen; increased fluid intake with frequent ingestion of simple and complex carbohydrates
All illnesses	30 g of simple carbohydrates (1 cup juice or regular soda) for lethargy; increase fluids. Hospital/physician evaluation for lethargy and decreased oral intake and urine output.
Vomiting	Repeat the dose if patient vomits within 1 h of medication intake. If patient vomits again, administer intramuscular injection of hydrocortisone 100 mg. If unable to tolerate fluids, call emergency services for evaluation following intramuscular injection.

Adapted from El-Maouche et al., 2018.

Prevention of adrenal crises - practical guidelines for patients

1. Always carry your steroid emergency card with you.
2. Situations that require glucocorticoid dose adjustment by yourself (triple dose of GC immediately):
   a Nausea with vomiting, diarrhea: in case no IV or IM injection is available, repeatedly take three times the oral dose of hydrocortisone despite vomiting as some absorption of hydrocortisone takes place very quickly! See a physician without delay! When oral medication is impossible (vomiting), rectal administration of glucocorticoids can be performed.
   b Intercurrent illness with fever >38.5 °C: triple hydrocortisone dose as long as body temperature continues to be elevated
3. Situations where you may benefit from glucocorticoid dose adjustment
   a Sustained psychological distress
   b Extensive physical exercise: Be cautious with glucocorticoid dose adjustment, in short-term high-intensity exercise hydrocortisone adaption has not been shown to be beneficial, but increase intake of sugar/carbohydrates [81].
4. Other situations: Extreme heat -— increase water and, in particular, salt intake
5. Mineralocorticoid dose can be continued as usual, no increase of dose necessary.

Situations that require glucocorticoid consultation of or dose adjustment by a physician

a. Surgical intervention[a]:
   Minor surgery (dentist, dermatologist): Doubling/tripling of daily dose
   Endoscopy: 60–100 mg hydrocortisone divided in two to three doses
   Major surgery: Commonly used practice is an i.v. bolus followed by a continuous infusion of hydrocortisone (200 mg per day)
b. Shock, severe trauma, coma, emergency surgery
c. Continued vomiting, diarrhea

[a] These represent standard suggestions and need to be adapted to the individual patient and situation by the care-taking physician.

From Reisch, 2015.

APPENDIX C. OPEN-LABEL EXTENSION TREATMENT PERIOD GLUCOCORTICOID AND CRINECERFONT DOSE ADJUSTMENT GUIDANCE (AFTER MONTH 18)

During the OLE, subjects may have their glucocorticoid doses adjusted as appropriate and tolerated to achieve the lowest glucocorticoid dose that maintains adequate disease control (in the opinion of the investigator). The glucocorticoid dose reduction will not require dose reduction below 8 mg/m^2/day hydrocortisone equivalents.

Starting at Month 18, all subjects will initially receive crinecerfont 100 mg bid. If the subject has inadequate disease control despite receiving glucocorticoid treatment at their target dose (in the opinion of the investigator), the crinecerfont dose may be increased to 100 mg qAM and 200 mg qPM (including at Month 18, after laboratory results are available). If the increased dose of 100 mg qAM and 200 mg qPM is not well tolerated, the dose may be reduced back to 100 mg bid. After the Month 24 visit, an alternative dosing regimen of once daily 200 mg qPM can be considered per the investigator. Crinecerfont doses should generally only be adjusted at or shortly after study visits (after laboratory results are available).

In the setting of inadequate disease control, if the glucocorticoid dose is at or above the target, an increase in the glucocorticoid dose should generally be considered only after the crinecerfont dose has been maximized for the subject. Changes to the glucocorticoid and crinecerfont doses should generally be separated by at least 1 month in order to assess the effect of each change.

Disease Control[a]	Current Glucocorticoid Dose	Current Crinecerfont Dose	Action
Adequate[a]	At target[a]	Any	Continue current glucocorticoid and crinecerfont doses; OR If taking crinecerfont 100 mg qAM AND 200 mg qPM, decrease crinecerfont dose to 100 mg bid; OR After Month 24, option to dose crinecerfont as 200 mg qPM
	Above target[a]	Any	Decrease glucocorticoid dose towards target[b]
Inadequate[a]	At or above target[a]	100 mg bid	Discuss compliance with glucocorticoid and study drug dosing; OR Increase crinecerfont dose to 100 mg qAM and 200 mg qPM
		200 mg qPM	Discuss compliance with glucocorticoid and study drug dosing; OR Change crinecerfont dose to 100 mg bid; OR Increase crinecerfont dose to 100 mg qAM and 200 mg qPM
		100 mg qAM AND 200 mg qPM[c]	Discuss compliance with glucocorticoid and study drug dosing; OR Increase glucocorticoid dose as clinically indicated
	Below target[a]	Any	Increase glucocorticoid dose towards target

[a] In the opinion of the investigator.
[b] Unless the investigator deems further attempts at dose reduction to not be advisable for that subject. After each glucocorticoid dose reduction, the site should contact the subject by telephone (within a week) to assess how the subject is tolerating the glucocorticoid dose reduction.
[c] Or the maximum crinecerfont dose tolerated by the subject.