CLINICAL STUDY PROTOCOL

Protocol Amendment No. 3 Final Version Date: 10 May 2022

Protocol Amendment No. 2 Final Version Date: 06 August 2021

Protocol Amendment No. 1 Final Version Date: 22 December 2020

Original Protocol Final Version Date: 22 September 2020

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

Study No.: NBI-74788-CAH2006

EudraCT #: 2020-004381-19

NCT04806451

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 Pediatric Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment

PROTOCOL No.: NBI-74788-CAH2006

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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10 May 2022
Date

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VP, Clinical Development - Endocrinology

LIST OF PERSONNEL

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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 Pediatric Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment

Protocol Number: NBI-74788-CAH2006

Phase of Development: 3

Study Center(s): Approximately 40 centers in the United States (US) and select ex-US countries

Objectives:

Primary:

- To evaluate the efficacy of crinecerfont, compared with placebo, in reducing adrenal steroid levels during a glucocorticoid-stable period.

Secondary:

- To evaluate the efficacy of crinecerfont, compared with placebo, in reducing daily glucocorticoid dosage while maintaining adrenal androgen control.
- To evaluate the effect of crinecerfont, compared with placebo, on clinical endpoints associated with supraphysiologic glucocorticoid dosing and androgen excess.
- To evaluate plasma concentrations of crinecerfont and metabolites.
- To assess the safety and tolerability of crinecerfont.

Methodology:

This is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of crinecerfont versus placebo administered twice daily (bid) with breakfast and evening meals for 28 weeks in approximately 81 pediatric subjects with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Eligible subjects will be randomly assigned in a 2:1 ratio (active:placebo) to either crinecerfont (25 mg bid via oral solution for subjects 10 to <20 kg, 50 mg bid via oral solution for subjects 20 to <55 kg, or 100 mg bid via oral capsules for subjects ≥55 kg) or matching placebo (oral solution placebo for subjects <55 kg and oral capsule placebo for subjects ≥55 kg). Dose assignment from Day 1 to Week 28 will be based on the subject's weight at Day 1. After the 28-week placebo-controlled treatment period, there will be a 24-week, open-label treatment period, during which all subjects will receive crinecerfont at doses based on their Week 28 body weight.

At Month 12 (Week 52), subjects will have the option to participate in an open-label extension (OLE). During the OLE, subjects will continue to receive crinecerfont at their weight-based dose, unless the subject has inadequate efficacy (in the opinion of the investigator), in which case their crinecerfont dose can be increased by doubling the evening dose. At Month 12, subjects can also elect to switch the crinecerfont formulation (oral solution or capsule) based on preference. Further guidance on changes to crinecerfont dosing in the OLE is provided in Appendix B. Subjects have the option to remain in the OLE until crinecerfont becomes commercially available, the Sponsor elects to discontinue development of crinecerfont for CAH or the Sponsor elects to discontinue the study.

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

Prior to any study-related procedures, written informed consent from subject's parent(s) or legal guardian(s) with signed and witnessed study subject assent will be obtained (which may be done remotely, if allowed and remote consenting procedures are in place), as required by the governing Institutional Review Board (IRB) or ethics committee and according to local laws and regulations. Subjects will undergo screening for up to 4 weeks (Week -4 to Day -1) to determine eligibility. The screening period can be extended by up to 4 weeks after discussion with and approval of the Medical Monitor to allow for delayed screening laboratory results that are needed to determine eligibility or to accommodate other extenuating logistical issues, such as scheduling. Prior to the blood sample collection during screening, subjects will be asked to take their evening glucocorticoid dose the night before prior to 2100 hours and hold their morning dose of glucocorticoid and fludrocortisone (if applicable). 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 28)

For visits at which blood samples are collected, subjects should take their evening glucocorticoid dose (if applicable) the night before prior to 2100 hours and hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug (after Day 1) until after predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast. For blood tests obtained at the study site, subjects should bring their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug (after Day 1) with them to the study site to take at the study site (with dosing to occur between approximately 0800 and 0830 hours with breakfast). Except for the screening visit, subjects should be fasting after midnight the night before until after the predose blood sample collection(s) but should be encouraged to drink water to avoid any hypovolemic status. Subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast with morning dosing.

Glucocorticoid-Stable Period

On Day 1, subjects who are ≥6 years of age with a body weight ≥20 kg should arrive at the study site for the serial blood sampling procedure and dosing, with dosing to occur between approximately 0800 and 0830 hours. Blood samples will be obtained serially over approximately 6 hours, with 2 baseline samples obtained approximately 15 minutes before the morning glucocorticoid dose and again immediately prior to the morning glucocorticoid dose administration (with dosing to occur between approximately 0800 and 0830 hours) and at 2, 3, 4, and 6 hours after the morning glucocorticoid dose, for a total of 6 blood sampling time points. Subjects who are <6 years of age or with a body weight <20 kg will have a blood sample collection prior to their morning glucocorticoid dose only (with dosing to occur between approximately 0800 and 0830 hours). For all subjects, salivary samples for adrenal androgens and precursors will be collected in the early morning (0600 hours), at approximately 0800 hours prior to the morning glucocorticoid dose, at approximately 3 and 6 hours after the morning glucocorticoid dose, and in the evening (within 30 minutes prior to the evening dose of glucocorticoid; if subject is not on an evening glucocorticoid dose, then prior to bedtime). The salivary samples at approximately 0800 hours prior to dosing and 3 and 6 hours after dosing should be collected at approximately the same time as any corresponding blood samples (as applicable). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose blood and salivary samples are collected. During the study, the exact timing of the blood and saliva samples, and the morning glucocorticoid, mineralocorticoid, and/or study drug dose (and breakfast), may be adjusted by ±1 hour to accommodate site and subject schedules if needed as long as this is done consistently per subject and the relative times between the sample(s) and the dose(s) are maintained.

Subjects will be randomized on Day 1 in a 2:1 ratio (active:placebo). Randomization will be stratified by pubertal stage (Tanner breast or genital stage 1 or 2 versus 3, 4 or 5) and sex. From the evening of the Day 1 visit (after all Day 1 assessments have been performed) until the morning of the Week 28 visit, all subjects will receive blinded study drug based on their Day 1 weight (25 mg bid via oral solution for subjects 10 to <20 kg, 50 mg bid via oral solution for subjects 20 to <55 kg, or 100 mg bid via oral capsules for subjects ≥55 kg). Study drug will be administered bid with the subject's breakfast and evening meals (each dose separated by approximately 12 hours).

From Day 1 until Week 4, subjects should maintain a stable glucocorticoid regimen to the extent possible, except for stress dosing if needed for illness or other significant physical stress, in order to assess the direct effect of study drug on adrenal androgens and precursors. Stress dosing of glucocorticoid (at any time during the study) can be based on guidance provided by the investigator, the subject's treating physician, or guidelines provided in the protocol (Appendix A).

Glucocorticoid-Adjustment Period

At the Week 4 visit, subjects ≥6 years of age with a body weight ≥20 kg should arrive at the study site for the serial blood sampling procedure and dosing, with dosing to occur between approximately 0800 and 0830 hours with breakfast. Blood samples will be obtained serially over approximately 6 hours, with 2 baseline samples (obtained approximately 15 minutes before and again immediately prior to the morning glucocorticoid and study drug dose, with dosing to occur between approximately 0800 and 0830 hour). Blood samples will also be obtained at 2, 3, 4, and 6 hours after dosing. Pharmacokinetic (PK) blood samples will be obtained at the same time points with the exception of only 1 required predose sample. Subjects who are <6 years of age or with a body weight <20 kg will have blood sample collection prior to the morning glucocorticoid and study drug dose only (with dosing to occur between approximately 0800 and 0830 hours with breakfast). For all subjects, salivary samples for adrenal androgens and precursors will be collected in the early morning (0600 hours), at

approximately 0800 hours prior to the morning glucocorticoid and study drug dose, at approximately 3 and 6 hours after the morning glucocorticoid and study drug dose, and in the evening (within 30 minutes prior to the evening dose of glucocorticoid; if subject is not on an evening glucocorticoid dose, then prior to bedtime). The salivary samples at approximately 0800 hours prior to dosing and 3 and 6 hours after dosing should be collected at approximately the same time as any corresponding blood samples (as applicable). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose blood and salivary samples are collected. During the study, the exact timing of the blood and saliva samples, and the morning glucocorticoid, mineralocorticoid, and/or study drug dose, may be adjusted by ±1 hour to accommodate site and subject schedules if needed, as long as the relative times between the sample(s) and the dose(s) are maintained.

From Week 4 until Week 28, the subject's glucocorticoid dose should be adjusted according to their androstenedione (A4) levels, with the goal to reach a target dose of 8 to 10 mg/m^2/day (in hydrocortisone dose equivalents adjusted for body surface area [BSA]) at Week 28, while A4 is controlled, ie, ≤120% of the baseline value or ≤ upper limit of normal (ULN), according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5). The calculation of glucocorticoid dose in hydrocortisone equivalents adjusted for BSA at Day 1 and Week 28 will be based on height and weight measurement at Day 1 and Week 28, respectively. BSA will be updated at Week 16 if height measurement is obtained at Week 16.

Glucocorticoid dose adjustments can occur in as few as 1 or up to 4 steps, depending on the starting and target glucocorticoid doses and the amount of dose adjustment at each step. Reductions in the glucocorticoid dose should follow the guideline of first reducing the most nonphysiologic glucocorticoid type and timing. The target glucocorticoid dose should be within the range of 8 to 10 mg/m^2/day while A4 levels are controlled and as long as there is no evidence of glucocorticoid insufficiency. The dose could be lower than this range if the investigator considers this appropriate depending on practical issues considered in clinical practice related to available dosage strengths but will not be mandated to be lower than this range. Before any glucocorticoid dose reduction is implemented, the investigator will evaluate the subject for any symptoms suggestive of glucocorticoid insufficiency using a standardized checklist and will arrange for follow-up if needed after the dose reduction.

The first glucocorticoid dose adjustment step at approximately Week 6 (or when the Week 4 lab results are available) should be guided by the change in A4 at Week 4 from baseline. A suggested guideline is provided in the table below, but the exact amount adjusted may differ from this guideline based on practical issues considered in clinical practice related to available dosage strengths. The investigator should contact the subject/guardian once the Week 4 lab results are available in order to provide guidance on the amount of the first glucocorticoid dose adjustment.

Percent Change From Baseline in Serum Androstenedione	**Androstenedione Level**	**Glucocorticoid Dose Adjustment**
Any increase	>ULN	Consider whether glucocorticoid dose needs to be increased
Any increase	≤ULN	Maintain current glucocorticoid dose
No change[a]	Any	Maintain current glucocorticoid dose
Decrease of ≤20%	Any	1 to 2 mg/m^2/day glucocorticoid dose decrease
Decrease of >20% to ≤40%	Any	2 to 3 mg/m^2/day glucocorticoid dose decrease
Decrease of >40%	Any	3 to 4 mg/m^2/day glucocorticoid dose decrease

ULN=upper limit of normal.
[a] Within reasonable variability in the opinion of the investigator.

A follow-up blood test (with salivary sample collection) should be arranged approximately 2 weeks later at Week 8 (at home or the study site).

If needed, subsequent glucocorticoid dose adjustment steps should occur when lab results are available (at approximately Week 10, Week 14, and Week 18) with follow-up blood and salivary tests at Week 12 (at home or the study site, if the glucocorticoid dose was previously modified), Week 16 (at home or the study site), and Week 20 (at home or the study site, if the glucocorticoid dose was previously modified). The target amount of glucocorticoid dose reduction at each step is approximately 1 to 4 mg/m^2/day but should be guided by the A4

level at the preceding blood test as well as on practical issues considered in clinical practice related to available dosage strengths.

Blood Test (Including Androstenedione)	Glucocorticoid Dose Adjustment Step
Week 8 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 10 (or when Week 8 labs available)
Week 12 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 14 (or when Week 12 labs available)
Week 16 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 18 (or when Week 16 labs available)
Week 20 (at home or the study site)	Potential GC dose increase (if needed) at approximately Week 22 (or when Week 20 labs available) to maintain androstenedione control

GC=glucocorticoid.

At all visits, if A4 is >120% of baseline and >ULN, increase glucocorticoid dose as appropriate in order to maintain A4 control.

For the Week 28 visit, subjects should hold their morning glucocorticoid and study drug dose until after the predose blood samples are collected, with dosing to occur between approximately 0800 and 0830 hours with breakfast. For subjects ≥6 years of age with a body weight ≥20 kg, another blood sample will be collected approximately 3 hours after the morning glucocorticoid and study drug dosing. For all subjects, salivary samples will be collected over the course of the day: at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid and study drug dosing and 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of glucocorticoid (if subject is not taking evening glucocorticoid dose, then prior to bedtime). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose salivary sample is collected.

Open-Label Treatment Period (Week 28 to Week 52)

From the evening of the Week 28 visit (after all Week 28 assessments have been performed) until the morning of the Week 52 visit, all subjects will receive active study drug based on their Week 28 weight (crinecerfont; 25 mg bid via oral solution for subjects 10 to <20 kg, 50 mg bid via oral solution for subjects 20 to <55 kg, or 100 mg bid via oral capsules for subjects ≥55 kg) with breakfast and evening meals. Subjects and investigators will remain blinded to subjects' randomized treatment group assignment during the entire study. From Week 28 until Week 32, subjects should maintain a stable glucocorticoid regimen to the extent possible, except for stress dosing if needed for illness or other significant physical stress. A blood sample will be collected at Week 32 (at home or the study site).

For subjects who are on >11 mg/m^2/day glucocorticoid dose (in hydrocortisone dose equivalents adjusted for BSA [based on weight and height at Week 28]) at Week 32, further adjustments in glucocorticoid dose should be made following guidelines similar to that used during the placebo-controlled period with the goal to reach a target dose of 8 to 10 mg/m^2/day in hydrocortisone dose equivalents adjusted for BSA at Week 52, while A4 is controlled. The calculation of glucocorticoid dose in hydrocortisone equivalents adjusted for BSA at Week 52 will be based on height and weight measurement at Week 52. BSA will be updated at Week 40 if height measurement is obtained at Week 40.

The first glucocorticoid dose adjustment step during this period (if done) should be guided by the serum A4 change at Week 32 (compared with Week 28), after the subject has been on open-label active study drug as well as stable glucocorticoid regimen (to the extent possible) for 4 weeks. A suggested guideline is provided below but the exact amount adjusted may differ from this guideline based on practical issues considered in clinical practice related to available dosage strengths. The investigator should contact the subject/guardian once the Week 32 lab results are available in order to provide guidance on the amount of the first glucocorticoid dose adjustment (if needed) during the open-label treatment period.

Percent Change from Week 28 in Serum Androstenedione	Androstenedione Level	Glucocorticoid Dose Adjustment
Any increase	>ULN	Consider whether glucocorticoid dose needs to be increased
Any increase	≤ULN	Maintain current glucocorticoid dose
No change[a]	Any	Maintain current glucocorticoid dose
Decrease of ≤20%	Any	1 to 2 mg/m^2/day glucocorticoid dose reduction
Decrease of >20% to ≤40%	Any	2 to 3 mg/m^2/day glucocorticoid dose reduction
Decrease of >40%	Any	3 to 4 mg/m^2/day glucocorticoid dose reduction

ULN=upper limit of normal.
[a] Within reasonable variability in the opinion of the investigator.

If the glucocorticoid dose is modified at approximately Week 34, a follow-up blood test (with salivary sample collection) should be arranged approximately 2 weeks later at Week 36 (at home or the study site).

If needed, subsequent glucocorticoid dose adjustments should occur at approximately Week 38 and Week 42 (or when lab results are available) with follow-up blood and salivary tests at Week 40 (at home or the study site) and Week 44 (at home or the study site, if the glucocorticoid dose was previously modified during the open-label treatment period). The target amount of glucocorticoid dose reduction at each step is approximately 1 to 4 mg/m^2/day but should be guided by the A4 level at the preceding blood test as well as practical issues considered in clinical practice related to available dosage strengths.

Blood Test (Including Androstenedione)	Glucocorticoid Dose Adjustment Step
Week 36 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 38 (or when Week 36 androstenedione result is available)
Week 40 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 42 (or when Week 40 androstenedione result is available)
Week 44 (at home or the study site)	Potential GC dose increase (if needed) at approximately Week 46 (or when Week 44 labs available) to maintain androstenedione control

GC=glucocorticoid; ULN=upper limit of normal.

At all visits, if A4 is >120% of baseline and >ULN, increase glucocorticoid dose as appropriate in order to maintain A4 control.

For the Week 52 visit, subjects should hold their morning glucocorticoid and study drug dose until after the predose blood samples are collected, with dosing to occur between approximately 0800 and 0830 hours with breakfast. For subjects ≥6 years of age with a body weight ≥20 kg, another blood sample will be collected approximately 3 hours after the morning glucocorticoid and study drug dose. For all subjects, salivary samples will be collected over the course of the day: at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid and study drug dosing and 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of glucocorticoid (if subject is not taking evening glucocorticoid dose, then prior to bedtime). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose salivary sample is collected.

Open-Label Extension for Continued Crinecerfont Access (Week 52 Onwards)

At Month 12 (Week 52), the subject's parent(s) or legal guardian(s) (or the subject, if the subject has reached the age of majority) will review applicable portions of the informed consent form (ICF) and the subject will review applicable portions of the assent form (if applicable) and confirm whether the subject will participate in the optional OLE.

During the OLE, subjects will continue to receive crinecerfont at the appropriate dose based on their body weight at each study visit (25 mg bid if weight is 10 to <20 kg, 50 mg bid if weight is 20 to <55 kg, 100 mg bid if weight

is ≥55 kg), unless the subject has inadequate efficacy (in the opinion of the investigator), in which case the crinecerfont dose can be increased by doubling the evening dose. Dose can be increased for inadequate efficacy once at the specified weight-based dose (eg, 50 mg BID can be increased to 50 mg qam and 100 mg qpm) but not further unless the subject crosses into the next weight category. If the investigator assesses the subject as having inadequate efficacy and in addition the subject has crossed into the next weight category, the crinecerfont dose should be increased first based on weight (not doubling the evening dose); efficacy should be assessed at the next scheduled study visit, and if efficacy remains inadequate the evening dose can be doubled at that time. If the crinecerfont dose is increased due to inadequate efficacy, a follow-up study visit should be performed approximately 1 month after the dose increase for efficacy, PK, and safety assessments. This follow-up study visit is not required for subjects who increase their dose due to crossing into the next weight category. Changes to the crinecerfont dose (whether based on crossing into the next weight category or based on inadequate efficacy) should generally only be made at scheduled study visits. Further guidance on changes to crinecerfont dosing in the OLE is provided in Appendix B.

At Month 12, subjects taking crinecerfont 50 mg bid or higher may elect to switch the crinecerfont formulation (oral solution or capsule) based on preference, eg, if the subject was receiving crinecerfont 50 mg bid oral solution from Week 28 to Month 12 but prefers capsule, they could switch to 50 mg bid capsule if remaining in the same weight category. Once this formulation preference is established at Month 12, the formulation should remain the same for the rest of the OLE (unless there is a tolerability issue, in which case the subject can revert back to the previous formulation, ideally within approximately 1 month).

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 investigator should contact the subject/guardian (within 2 weeks) to assess how the subject is tolerating the glucocorticoid dose reduction. 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.

Starting at Month 12, study visits during the OLE will occur every 6 months. At each OLE study visit (including visits performed approximately 1 month after a dose increase for inadequate efficacy), subjects should hold their morning glucocorticoid and study drug dose until after the predose blood samples are collected, with dosing to occur between approximately 0800 and 0830 hours with breakfast. At Month 24 and every 12 months thereafter, for subjects ≥6 years of age with a body weight ≥20 kg, another blood sample will be collected approximately 3 hours after the morning glucocorticoid and crinecerfont dose. In addition, for all subjects, salivary samples will be collected over the course of the day at Month 24, every 12 months thereafter and at the early termination visit: at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid and study drug dosing and 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of glucocorticoid (if subject is not taking evening glucocorticoid dose, then prior to bedtime). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose salivary sample is collected.

The study will continue, and subjects have the option to remain in the OLE until crinecerfont becomes commercially available, the Sponsor elects to discontinue development of crinecerfont for CAH, or the Sponsor elects to discontinue the study.

Follow-up Period

A final posttreatment visit will be conducted approximately 4 weeks after subject's final dose of study drug. This visit is not required if the subject transitions during the OLE to 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, during the study, and follow-up) should occur at approximately the same time in the morning to standardize time of day for blood draws. All assessments during the core study as well as the OLE that are performed based on the subject's age should be based on the age at time of initial informed consent, unless otherwise specified.

The Week 4 visit will have a visit window of ±5 days, and subsequent visits through Week 52 will have a visit window of ±7 days. During the OLE, visits will have a visit window of ±14 days. All Week 28 assessments

should be completed before a subject begins the open-label treatment period, and all Week 52 assessments should be completed before a subject begins the OLE. All assessments need not be conducted on the same day, but all assessments for a given visit must be completed within the visit window. If a subject's glucocorticoid regimen is adjusted due to stress dosing, the subject should resume their glucocorticoid dosing regimen for at least 3 days before their next scheduled lab test if the duration of stress dosing is 3 days or less), and for at least 7 days before their next scheduled lab test if the duration of stress dosing is ≥4 days (of note, this 3- or 7-day window supersedes all other visit windows).

An independent Data Monitoring Committee will periodically review unblinded study data to ensure the safety and well-being of study subjects and to confirm observed exposures are consistent with expected target exposures.

Study population: Approximately 81 female and male subjects, 2 to 17 years of age at the time of signing the initial informed consent, 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 60 weeks, plus a variable amount of time in the OLE (estimated average of approximately 24 months), including 4 weeks for screening, 28 weeks of blinded placebo-controlled treatment, 24 weeks of open-label treatment, a variable amount of time of OLE treatment, and 4 weeks of follow-up.

Investigational product, dosage and mode of administration: Crinecerfont (25 mg bid via oral solution for subjects 10 to <20 kg, 50 mg bid via oral solution for subjects 20 to <55 kg, or 100 mg bid via oral capsules for subjects ≥55 kg) with subjects' breakfast and evening meals (each dose separated by approximately 12 hours) from Day 1 to Month 12. During the OLE, the crinecerfont dose should be based on the subject's weight at the study visit (25 mg bid if weight is 10 to <20 kg, 50 mg bid if weight is 20 to <55 kg, 100 mg bid if weight is ≥55 kg), unless the subject has inadequate efficacy (in the opinion of the investigator), in which case the crinecerfont dose can be increased by doubling the evening dose. At Month 12, subjects participating in the OLE could elect to switch crinecerfont formulation based on preference. Each crinecerfont oral capsule contains 50 mg of crinecerfont. The oral solution contains 50 mg of crinecerfont per 1 mL and will be administered via a graduated oral dosing syringe.

Reference therapy, dose and mode of administration, batch number: Placebo oral solution is identical in appearance and flavored identically to crinecerfont oral solution. Placebo capsules are identical in appearance to crinecerfont capsules. Placebo oral solution and capsules will be used to maintain the blind during the placebo-controlled treatment period.

Criteria for evaluation:

Efficacy:

- Hormone measurements: A4 (serum and saliva), 17-hydroxyprogeterone (17-OHP; serum and saliva), adrenocorticotropic hormone (ACTH) (plasma), luteinizing hormone (LH; serum), follicle-stimulating hormone (FSH; serum), testosterone (serum and saliva), cortisol (serum and saliva), plasma renin activity (PRA) (measured upright)
- Daily glucocorticoid regimen expressed in hydrocortisone dose equivalents adjusted for BSA ($mg/m^2/day$)
- Body weight and body mass index (absolute and standard deviation score [SDS] units)
- Growth (assessed as Bayley-Pinneau predicted adult height, height, and height velocity in absolute and SDS units; only in growing subjects)
- Bone age based on x-ray (assessed in absolute and SDS units, also adjusted for chronologic age; only for subjects not at adult height)
- Fasting lipid panel and homeostatic model assessment of insulin resistance (HOMA-IR) based on fasting glucose and insulin levels
- Menstrual Cycle Questionnaire (only females who have undergone menarche and are not on hormonal or intrauterine device contraceptives)
- Hirsutism (only for female subjects) and acne scales
- Testicular ultrasounds (to detect adrenal rest tumors; only in male subjects)

Patient and Caregiver Reported Outcomes:

- EQ-5D-Y for ages 8 to 15 years; EQ-5D-5L for ages 16 to 17 years
- Pediatric Quality of Life Instrument (PedsQL)
- PedsQL Family Impact Module

Pharmacokinetics:

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

Other:

- Study drug palatability/ease of administration (palatability will be assessed by subjects ≥6 years of age, and ease of administration will be assessed by caregivers for subjects <6 years of age)
- Cytochrome P450 (CYP) 21A2 genotyping

Safety:

- Adverse events (AEs) (including events requiring glucocorticoid stress dosing)
- Clinical laboratory tests (chemistry, hematology, coagulation, fasting glucose, urinalysis)
- Vital signs
- Physical examinations, including height, weight, and Tanner stage
- 6- or 12-lead electrocardiograms (ECGs)
- Brief Psychiatric Rating Scale, Children's Version
- Columbia-Suicide Severity Rating Scale (only for subjects ≥6 years of age)

Study Endpoints and Statistical Analysis: The primary endpoint is the change from baseline to Week 4 in serum A4. The first key secondary endpoint is the change from baseline to Week 4 in serum 17-OHP. The second key secondary endpoint is the percent change from baseline to Week 28 in glucocorticoid daily dose (in hydrocortisone dose equivalents adjusted for BSA [mg/m^2/day]), while Week 28 serum A4 is ≤120% of the baseline value or ≤ULN, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5). These endpoints will be analyzed using an analysis of covariance model and will include treatment group (crinecerfont versus placebo), stratification factors used in the randomization and, as appropriate, baseline value. The overall type I error of 0.05 will be controlled by testing the primary, first key secondary, and second key secondary endpoints sequentially in this order.

Secondary endpoints will include:

- The achievement of a reduction in glucocorticoid daily dose to physiologic levels (≤11 mg/m^2/day in hydrocortisone dose equivalent adjusted for BSA) at Week 28, while Week 28 serum A4 is ≤120% of the baseline value or ≤ULN, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5).
- Change from baseline to Week 28 in body mass index SDS.
- Change from baseline to Week 28 in mean 24-hour salivary 17-OHP.
- Acceptability and palatability of the study drug at Week 4.
- Ratio of the change in bone age from baseline to Week 28 to the change in chronologic age from baseline to Week 28 (in subjects not at adult height).
- Change from baseline to Week 52 in Bayley-Pinneau predicted adult height SDS (in subjects not at adult height).

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

17-OHP	17-hydroxyprogesterone
A4	androstenedione
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the plasma concentration versus time curve from time 0 to infinity
bid	twice daily
BPRS-c	Brief Psychiatric Rating Scale for Children
BSA	body surface area
CAH	congenital adrenal hyperplasia
CDC	Center for Disease Control and Prevention
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CRF_1	corticotropin-releasing factor type 1 receptor
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450 enzyme
DMC	Data Monitoring Committee
DSPV	Drug Safety and Pharmacovigilance
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
FAS	full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
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
IRT	interactive response technology
LH	luteinizing hormone
MDD	major depressive disorder
NBI	Neurocrine Biosciences, Inc.
NOAEL	no observed adverse effect level

OLE	open-label extension
PedsQL	Pediatric Quality of Life Instrument
PI	Principal Investigator
PK	pharmacokinetic(s)
PRA	plasma renin activity
qd	once daily
qhs	once daily at bedtime
QTcF	QT interval corrected for heart rate using Fridericia's correction
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SDS	standard deviation score
T4	thyroxine
TART	testicular adrenal rest tumor
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell

4. ETHICS

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 (NBI-74788) is a selective corticotropin-releasing factor type 1 receptor (CRF_1) antagonist that is being developed as a novel oral treatment for patients with classic congenital adrenal hyperplasia (CAH), a rare autosomal recessive disorder characterized by deficiency of an enzyme (21-hydroxylase in approximately 95% of cases) involved in adrenal steroidogenesis that results in deficiency of cortisol and often also aldosterone. One clinical manifestation of the absence of cortisol that occurs in CAH is the loss of the normal negative feedback inhibition of cortisol on pituitary adrenocorticotropic hormone (ACTH) secretion. Increased ACTH levels cause adrenal hyperplasia and increased production of steroid precursors that are shunted to production of adrenal androgens because of the 21-hydroxylase deficiency. The overproduction of androgens leads to virilization of female infants, and the over-accumulation of ACTH is associated with the formation of testicular adrenal rest tumors (TARTs) in males. Since 21-hydroxylase is also used for the biosynthesis of mineralocorticoids, these patients typically suffer from some degree of aldosterone deficiency ranging from a hypovolemic stimulus to ACTH (and resulting hyperandrogenism) to dehydration and death due to salt-wasting in the most severe cases.

Pediatric CAH patients from birth through adolescence appear to be the most vulnerable population and represent the subgroup of patients with the greatest unmet medical need (Cheng and Speiser, 2012; Merke and Poppas, 2013). Even with newborn detection and appropriate treatment from early infancy, excessive androgen production in pediatric patients can result in advanced skeletal maturation, premature growth plate fusion, early or precocious puberty, and adult height shorter than genetic potential as well as other signs of hyperandrogenism including clitoromegaly, hirsutism, acne, and amenorrhea in females.

Since the introduction of glucocorticoid and mineralocorticoid therapies in the 1950s, patients with classic CAH due to 21-hydroxylase deficiency generally survive infancy and childhood through to adolescence and adulthood. Glucocorticoid treatment is used not only to treat the adrenal insufficiency, but also to suppress ACTH and the downstream production of excess androgens. However, lifetime glucocorticoid (and mineralocorticoid) treatment alone is often not sufficient to control elevated androgen levels and sequelae of the disease, even when glucocorticoid is dosed at supraphysiological levels, as commonly occurs. The standard-of-care treatment itself, namely glucocorticoid treatment at supraphysiologic doses, presents its own significant health outcome risks and challenges for CAH patients, including iatrogenic Cushing's syndrome with obesity, hypertension, insulin resistance, diabetes, increased cardiovascular risk, decreased bone mineral density, and (in children) growth suppression (Elnecave et al., 2008; King et al., 2006; Migeon and Wisniewski, 2001). Importantly, there have been no new therapies developed for classic CAH since the 1950s and thus no other options besides glucocorticoid (and mineralocorticoid) treatment to manage the androgen excess.

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 glucocorticoid. 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). In single-dose studies, no signs of acute toxicity were observed in rats following a single administration up to 2000 mg/kg with the salt, and the maximal tolerated dose determined with the crinecerfont free base in rats was considered to be above 2000 mg/kg. Additionally, crinecerfont was well tolerated in male dogs up to 1500 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 a no observed adverse effect level (NOAEL) of at least 15 mg/kg/day in the mouse, 15 mg/kg/day in the rat, and 1000 mg/kg/day in the dog. These NOAEL doses yielded plasma exposures that were comparable with 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 2000 mg/kg/day in pregnant rats and up to 500 mg/kg/day in pregnant rabbits. Based on these results, crinecerfont is assessed as being unlikely to have human teratogenicity/fetotoxicity potential.

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.

A summary of crinecerfont clinical development data available to date is summarized below:

Crinecerfont has been administered to approximately 800 adult human subjects in 16 completed Phase 1 and Phase 2 studies. Data are available from more than 400 healthy male and female subjects exposed to crinecerfont in 10 completed Phase 1 single-dose and 4 completed repeat-dose studies. Additionally, 361 male and female adults with major depressive disorder (MDD) received crinecerfont (20, 50, and 100 mg) for up to 8 weeks in an active- (escitalopram) and placebo-controlled Phase 2 study. In a Phase 2 dose-finding study, 18 male and female adults with CAH received crinecerfont (50 mg once daily [qd] at bedtime [qhs; n=8], 100 mg qhs [n=7], 100 mg qd with dinner [n=8], or 100 mg twice daily [bid; n=8]) for 14 days (note: some subjects participated in more than 1 dose cohort.) Additionally, 8 adolescents (14 to 16 years of age) with CAH have been treated with crinecerfont 50 mg bid for 14 days in a clinically complete Phase 2 study.

Absorption of crinecerfont is relatively slow with low permeability. Exposure is optimized when administered with food, which improves bioavailability and decreases variability. Steady state levels are reached after 7 days of treatment. Although there is a long terminal elimination phase half-life of approximately 20 days, the effective half-life is approximately 14 hours based on a low accumulation ratio with repeated dosing. Following dosing to steady state, plasma

concentrations are less than 5% of maximum plasma concentration (C_{max}) by 4 weeks after the last dose. In vitro metabolism studies indicate that crinecerfont is mainly metabolized in the liver by cytochrome P450 (CYP) 3A4 and CYP2B6. Drug-drug interaction studies with midazolam and with oral contraceptives indicated no significant interaction with these medications. Concomitant administration of a single 100 mg dose of crinecerfont capsules with repeated administration of rifampin, a strong inducer of CYP3A4 and moderate inducer of CYP2B6, led to a 23% decrease in C_{max} and a 62% decrease in area under the plasma concentration versus time curve from time 0 to infinity ($AUC_{0-\infty}$) of crinecerfont compared with administration of crinecerfont alone, indicating that rifampin treatment decreases overall crinecerfont exposure. Thus, concomitant administration of strong CYP3A4 and CYP2B6 inducers should be avoided with crinecerfont. Crinecerfont is not considered to have clinically meaningful inhibition of any CYP or drug transporters BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OCT2, MATE1, or MATE2-K, and is not a substrate of the major drug transporters P-glycoprotein, OATP1B1, or OATP1B3.

Crinecerfont has been generally well tolerated in the 16 completed Phase 1 and Phase 2 studies of healthy subjects (14 studies) and subjects with MDD or CAH (2 studies) conducted to date. No dose-limiting toxicities have been identified throughout the dose range in the clinical trials, including single-dose (up to 800 mg) and multiple-dose (up to 400 mg/day for 16 days) studies. In a pooled analysis of subjects across all completed clinical trials who received crinecerfont, the most common (≥5% subject incidence) treatment-emergent adverse events (TEAEs) were headache (17.8% of subjects overall) and nausea (7.6% of subjects overall), while TEAEs in the range of 2% to 5% were dizziness, diarrhea, postural dizziness, somnolence, dry mouth, fatigue, nasopharyngitis, upper respiratory tract infection, blood creatine kinase increase, back pain and contact dermatitis. No apparent dose relationship was observed in the incidence of TEAEs. There were no safety concerns for clinical laboratory parameters including hormone levels (ACTH, cortisol, testosterone, thyroid-stimulating hormone [TSH], free triiodothyronine, free thyroxine [T4], prolactin, growth hormone, luteinizing hormone [LH], and follicle-stimulating hormone [FSH]), vital signs, and electrocardiogram (ECG) parameters.

In a Phase 2 randomized, double-blind, placebo-controlled study of 361 subjects with MDD treated for 8 weeks with crinecerfont 20 mg, 50 mg, or 100 mg/day versus placebo or escitalopram, the most common TEAEs were headache, nausea, dry mouth, dizziness, somnolence, constipation, fatigue, and neutropenia. All of these events had incidence <10% except for headache and nausea, which had incidence that was generally <20% and was slightly higher with crinecerfont than placebo but similar to escitalopram. The incidence of treatment-emergent serious adverse events (SAEs) was lower with all crinecerfont doses (0.8%) vs. placebo (1.7%) and escitalopram group (4.3%). The percentage of subjects who discontinued study drug due to a TEAE was slightly higher in the crinecerfont 100 mg group (12.5%) than in the other treatment groups (9.0% in crinecerfont 50 mg, 8.4% in crinecerfont 20 mg, 8.7% in escitalopram 10 mg, and 5.2% in placebo). The percentage of subjects who had any suicidal ideation (based on Columbia-Suicide Severity Rating Scale [C-SSRS] assessment) during the study was similar across treatment groups (20 mg: 26.5%, 50 mg: 18.0%, 100 mg: 20.5%, placebo: 18.4%, escitalopram: 14.9%).

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 either 25, 50, or 100 mg bid (25 mg bid via oral solution for subjects 10 to <20 kg, 50 mg bid via oral solution for subjects 20 to <55 kg, or 100 mg bid via oral capsules for subjects ≥55 kg) relative to placebo in pediatric subjects with classic CAH due to 21-hydroxylase deficiency. These doses were selected based on population pharmacokinetic (PK) modelling to match exposures in these respective weight groups to a 100 mg bid regimen in adults, which was selected for evaluation in the ongoing Phase 3 study in adult CAH subjects based on data from the Phase 2 Study NBI-74788-CAH2001. In addition, during an optional open-label extension (OLE) for continued access to crinecerfont, subjects with inadequate efficacy can have their dose increased by doubling the evening dose.

Total daily doses of crinecerfont 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 adult 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 adult subjects with classic CAH received crinecerfont 50 mg at bedtime, 100 mg at bedtime, 100 mg every evening, or 100 mg bid. This study demonstrated that administration of 100 mg bid crinecerfont led to meaningful median reductions in ACTH and 17-hydroxyprogesterone (17-OHP; 54% to 75% from baseline) as well as androstenedione (A4) concentrations in subjects with classic CAH after 14 days of treatment. A dose-response for A4 was observed with approximately 20% median reduction from baseline with the 50 mg dose, approximately 40% with each of the 100 mg qd doses, and approximately 60% with the 100 mg bid dose. Therefore, plasma exposure resulting from a 100 mg bid dosing in adults is expected to provide maximal reduction in adrenal androgens. Crinecerfont was well tolerated at all dose regimens evaluated with no evidence of dose-related increase in frequency of adverse events (AEs). AEs were mostly mild, with 1 SAE (assessed as unrelated to study drug) of cholelithiasis reported in a subject receiving 100 mg at bedtime. The most common TEAEs (ie, reported in ≥2 subjects overall) were headache, upper respiratory tract infection, fatigue, contusion, insomnia, nasopharyngitis, pyrexia, and nausea. There were no safety concerns related to laboratory, vital signs, or ECG results.

Based on population PK modeling with exposures matched to 100 mg bid in adults and following an allometric scaling approach, pediatric subjects will be categorized into the following weight groups: 10 to <20 kg, 20 to <55 kg, and ≥55 kg. Twice-daily dosing regimens for each weight group that result in exposures comparable to a 100 mg bid dose for adults are provided in Table 1. Crinecerfont oral solution (50 mg/mL) has a demonstrated relative bioavailability of approximately 87% and similar variability in PK parameters compared with the 50 mg capsule.

Table 1: Crinecerfont Dose Regimen by Weight Group, Day 1 to Week 52

Body Weight (kg)	Dose Regimen	Each Dosage		Total Daily Dose
		qam	qpm	
10 to <20	25 mg bid	0.5 mL oral solution	0.5 mL oral solution	50 mg
20 to <55	50 mg bid	1.0 mL oral solution	1.0 mL oral solution	100 mg
≥55	100 mg bid	2 × 50 mg capsules	2 × 50 mg capsules	200 mg

bid=twice daily; qam=in the morning; qpm=in the evening.

At Month 12, subjects participating in the OLE who are receiving crinecerfont ≥50 mg bid may elect to switch crinecerfont formulation based on preference. Starting at Month 12, if the subject has inadequate efficacy (in the opinion of the investigator), the crinecerfont dose can be increased by doubling the evening dose (evening dose can only be doubled once per weight category for a given subject) (Table 2). This alternate dose regimen is expected to match exposures in adults receiving a total daily dose of 300 mg of crinecerfont. The crinecerfont 300 mg total daily dose was well tolerated in a 28-day study in healthy adult volunteers (NBI-74788-1724) and is currently being evaluated in adults with CAH participating in an ongoing Phase 3 study (NBI-74788-CAH3003).

Table 2: Crinecerfont Dose Regimen by Weight Group, Open-Label Extension

Body Weight (kg)	Dose Regimen	Each Dosage		Total Daily Dose
		qam	qpm	
Weight-based dosing				
10 to <20	25 mg bid	0.5 mL oral solution	0.5 mL oral solution	50 mg
20 to <55	50 mg bid	1.0 mL oral solution	1.0 mL oral solution	100 mg
		OR		
		1 × 50 mg capsule	1 × 50 mg capsule	
≥55	100 mg bid	2.0 mL oral solution	2.0 mL oral solution	200 mg
		OR		
		2 × 50 mg capsules	2 × 50 mg capsules	
For subjects who have their evening dose doubled				
10 to <20	25 mg qam 50 mg qpm	0.5 mL oral solution	1.0 mL oral solution	75 mg
20 to <55	50 mg qam 100 mg qpm	1.0 mL oral solution	2.0 mL oral solution	150 mg
		OR		
		1 × 50 mg capsule	2 × 50 mg capsules	
≥55	100 mg qam 200 mg qpm	2.0 mL oral solution	4.0 mL oral solution	300 mg
		OR		
		2 × 50 mg capsules	4 × 50 mg capsules	

bid=twice daily; qam=in the morning; qpm=in the evening.

5.4. End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data used for the primary endpoint, whether the study concluded as planned or was terminated early. The planned primary completion date for this study is the date when the last subject has completed the assessments for Week 4. If the study is terminated early, then the primary completion date will be the date of the last visit for the last subject in the study.

End of Study: The end of study is defined as the date of the last visit of the last subject or last scheduled procedure shown in the schedule of assessments for the last subject in the study globally.

6. STUDY OBJECTIVES

6.1. Primary

The primary objective of this study is:

- To evaluate the efficacy of crinecerfont, compared with placebo, in reducing adrenal steroid levels during a glucocorticoid-stable period.

6.2. Secondary

The secondary objectives of this study are the following:

- To evaluate the efficacy of crinecerfont, compared with placebo, in reducing daily glucocorticoid dosage while maintaining adrenal androgen control.
- To evaluate the effect of crinecerfont, compared with placebo, on clinical endpoints associated with supraphysiologic glucocorticoid dosing and androgen excess.
- To evaluate plasma concentrations of crinecerfont and metabolites.
- To assess the safety and tolerability of crinecerfont.

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 evening meals for 28 weeks in approximately 81 pediatric subjects with classic CAH due to 21-hydroxylase deficiency. Eligible subjects will be randomly assigned in a 2:1 ratio (active:placebo) to either crinecerfont (25 mg bid via oral solution for subjects 10 to <20 kg, 50 mg bid via oral solution for subjects 20 to <55 kg, or 100 mg bid via oral capsules for subjects ≥55 kg) or matching placebo (oral solution placebo for subjects <55 kg and oral capsule placebo for subjects ≥55 kg). Dose assignment from Day 1 to Week 28 will be based on the subject's weight at Day 1. After the 28-week placebo-controlled treatment period, there will be a 24-week, open-label treatment period, during which all subjects will receive crinecerfont at doses based on their Week 28 body weight.

At Month 12 (Week 52), subjects will have the option to participate in an OLE (Section 9.11.2). During the OLE, subjects will continue to receive crinecerfont at their weight-based dose, unless the subject has inadequate efficacy (in the opinion of the investigator), in which case their crinecerfont dose can be increased by doubling the evening dose. At Month 12, subjects can also elect to switch the crinecerfont formulation (oral solution or capsule) based on preference. Further guidance on changes to crinecerfont dosing in the OLE is provided in Appendix B. Subjects have the option to remain in the OLE until crinecerfont becomes commercially available, the Sponsor elects to discontinue development of crinecerfont for CAH, or the Sponsor elects to discontinue the study.

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

Prior to any study-related procedures, written informed consent from subject's parent(s) or legal guardian(s) with signed and witnessed study subject assent will be obtained (which may be done remotely, if allowed and remote consenting procedures are in place), as required by the governing IRB or ethics committee and according to local laws and regulations. Subjects will undergo screening for up to 4 weeks (Week -4 to Day -1) to determine eligibility. The screening period can be extended by up to 4 weeks after discussion with and approval of the Medical Monitor to allow for delayed screening laboratory results that are needed to determine eligibility or to accommodate other extenuating logistical issues, such as scheduling. Prior to the blood sample collection during screening, subjects will be asked to take their evening glucocorticoid dose the night before prior to 2100 hours and hold their morning dose of glucocorticoid and fludrocortisone (if applicable), but do not need to be fasting. 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.

7.2. Randomized, Double-Blind, Placebo-Controlled Treatment Period (Day 1 up to Week 28)

For visits at which blood samples are collected, subjects should take their evening glucocorticoid dose (if applicable) the night before prior to 2100 hours and hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug (after Day 1) until after predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast. For blood tests obtained at the study site, subjects should bring their morning dose of

glucocorticoid, fludrocortisone (if applicable), and study drug (after Day 1) with them to the study site to take at the study site (with dosing to occur between approximately 0800 and 0830 hours with breakfast). Except for the screening visit, subjects should be fasting after midnight the night before until after the predose blood sample collection(s) but should be encouraged to drink water to avoid any hypovolemic status. Subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast with morning dosing.

Glucocorticoid-Stable Period

On Day 1, subjects who are ≥6 years of age with a body weight ≥20 kg should arrive at the study site for the serial blood sampling procedure and dosing, with dosing to occur between approximately 0800 and 0830 hours. Blood samples will be obtained serially over approximately 6 hours, with 2 baseline samples obtained approximately 15 minutes before the morning glucocorticoid dose and again immediately prior to the morning glucocorticoid dose administration (with dosing to occur between approximately 0800 and 0830) and at 2, 3, 4, and 6 hours after the morning glucocorticoid dose, for a total of 6 blood sampling time points. Subjects who are <6 years of age or with a body weight <20 kg will have a blood sample collection prior to their morning glucocorticoid dose only (with dosing to occur between approximately 0800 and 0830 hours). For all subjects, salivary samples for adrenal androgens and precursors will be collected in the early morning (0600 hours), at approximately 0800 hours prior to the morning glucocorticoid dose, at approximately 3 and 6 hours after the morning glucocorticoid dose, and in the evening (within 30 minutes prior to the evening dose of glucocorticoid; if subject is not on an evening glucocorticoid dose, then prior to bedtime). The salivary samples at approximately 0800 hours prior to dosing and 3 and 6 hours after dosing should be collected at approximately the same time as any corresponding blood samples (as applicable). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose blood and salivary samples are collected. During the study, the exact timing of the blood and saliva samples, and the morning glucocorticoid, mineralocorticoid, and/or study drug dose (and breakfast), may be adjusted by ±1 hour to accommodate site and subject schedules if needed as long as this is done consistently per subject and the relative times between the sample(s) and the dose(s) are maintained.

Subjects will be randomized on Day 1 in a 2:1 ratio (active:placebo). Randomization will be stratified by pubertal stage (Tanner breast or genital stage 1 or 2 versus 3, 4, or 5) and sex. From the evening of the Day 1 visit (after all Day 1 assessments have been performed) until the morning of the Week 28 visit, all subjects will receive blinded study drug based on their Day 1 weight (25 mg bid via oral solution for subjects 10 to <20 kg, 50 mg bid via oral solution for subjects 20 to <55 kg, or 100 mg bid via oral capsules for subjects ≥55 kg). Study drug will be administered bid with the subject's breakfast and evening meals (each dose separated by approximately 12 hours).

From Day 1 until Week 4, subjects should maintain a stable glucocorticoid regimen to the extent possible, except for stress dosing if needed for illness or other significant physical stress, in order to assess the direct effect of study drug on adrenal androgens and precursors. Stress dosing of glucocorticoid (at any time during the study) can be based on guidance provided by the investigator, the subject's treating physician, or guidelines provided in the protocol (Appendix A).

Glucocorticoid-Adjustment Period

At the Week 4 visit, subjects ≥6 years of age with a body weight ≥20 kg should arrive at the study site for the serial blood sampling procedure and dosing, with dosing to occur between approximately 0800 and 0830 hours with breakfast. Blood samples will be obtained serially over approximately 6 hours, with 2 baseline samples (obtained approximately 15 minutes before and again immediately prior to the morning glucocorticoid and study drug dose, with dosing to occur between approximately 0800 and 0830 hours with breakfast). Blood samples will also be obtained at 2, 3, 4, and 6 hours after dosing. PK blood samples will be obtained at the same time points with the exception of only 1 required predose sample. Subjects who are <6 years of age or with a body weight <20 kg will have blood sample collection prior to the morning glucocorticoid and study drug dose only (with dosing to occur between approximately 0800 and 0830 hours with breakfast). For all subjects, salivary samples for adrenal androgens and precursors will be collected in the early morning (0600 hours), at approximately 0800 hours prior to the morning glucocorticoid and study drug dose, at approximately 3 and 6 hours after the morning glucocorticoid and study drug dose, and in the evening (within 30 minutes prior to the evening dose of glucocorticoid; if subject is not on an evening glucocorticoid dose, then prior to bedtime). The salivary samples at approximately 0800 hours prior to dosing and 3 and 6 hours after dosing should be collected at approximately the same time as any corresponding blood samples (as applicable). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose blood and salivary samples are collected. During the study, the exact timing of the blood and saliva samples, and the morning glucocorticoid, mineralocorticoid, and/or study drug dose, may be adjusted by ±1 hour to accommodate site and subject schedules if needed, as long as the relative times between the sample(s) and the dose(s) are maintained.

From Week 4 until Week 28, the subject's glucocorticoid dose should be adjusted according to their A4 levels, with the goal to reach a target dose of 8 to 10 mg/m^2/day (in hydrocortisone dose equivalents adjusted for body surface area [BSA]) at Week 28, while A4 is controlled, ie, ≤120% of the baseline value or ≤ upper limit of normal (ULN), according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5). The calculation of glucocorticoid dose in hydrocortisone equivalents adjusted for BSA at Day 1 and Week 28 will be based on height and weight measurement at Day 1 and Week 28, respectively. BSA will be updated at Week 16 if height measurement is obtained at Week 16.

Glucocorticoid dose adjustments can occur in as few as 1 or up to 4 steps, depending on the starting and target glucocorticoid doses and the amount of dose adjustment at each step. Reductions in the glucocorticoid dose should follow the guideline of first reducing the most nonphysiologic glucocorticoid type and timing. The target glucocorticoid dose should be within the range of 8 to 10 mg/m^2/day while A4 levels are controlled and as long as there is no evidence of glucocorticoid insufficiency. The dose could be lower than this range if the investigator considers this appropriate depending on practical issues considered in clinical practice related to available dosage strengths but will not be mandated to be lower than this range. Before any glucocorticoid dose reduction is implemented, the investigator will evaluate the subject for any symptoms suggestive of glucocorticoid insufficiency using a standardized checklist and will arrange for follow-up if needed after the dose reduction.

The first glucocorticoid dose adjustment step at approximately Week 6 (or when the Week 4 lab results are available) should be guided by the change in A4 at Week 4 from baseline. A

suggested guideline is provided in Table 3, but the exact amount adjusted may differ from this guideline based on practical issues considered in clinical practice related to available dosage strengths. The investigator should contact the subject/guardian once the Week 4 lab results are available in order to provide guidance on the amount of the first glucocorticoid dose adjustment.

Table 3: Guide for Glucocorticoid Dose Adjustments During the Randomized, Placebo-Controlled Treatment Period

Percent Change From Baseline in Serum Androstenedione	Androstenedione Level	Glucocorticoid Dose Adjustment
Any increase	>ULN	Consider whether glucocorticoid dose needs to be increased
Any increase	≤ULN	Maintain current glucocorticoid dose
No change[a]	Any	Maintain current glucocorticoid dose
Decrease of ≤20%	Any	1 to 2 mg/m^2/day glucocorticoid dose decrease
Decrease of >20% to ≤40%	Any	2 to 3 mg/m^2/day glucocorticoid dose decrease
Decrease of >40%	Any	3 to 4 mg/m^2/day glucocorticoid dose decrease

ULN=upper limit of normal.
[a] Within reasonable variability in the opinion of the investigator.

A follow-up blood test (with salivary sample collection) should be arranged approximately 2 weeks later at Week 8 (at home or the study site).

If needed, subsequent glucocorticoid dose adjustment steps should occur when lab results are available (at approximately Week 10, Week 14, and Week 18) with follow-up blood and salivary tests at Week 12 (at home or the study site, if the glucocorticoid dose was previously modified), Week 16 (at home or the study site), and Week 20 (at home or the study site, if the glucocorticoid dose was previously modified) (Table 4). The target amount of glucocorticoid dose reduction at each step is approximately 1 to 4 mg/m^2/day but should be guided by the A4 level at the preceding blood test as well as on practical issues considered in clinical practice related to available dosage strengths.

Table 4: Schedule for Blood Tests and Potential Glucocorticoid Dose Adjustments During the Randomized, Placebo-Controlled Treatment Period

Blood Test (Including Androstenedione)	Glucocorticoid Dose Adjustment Step
Week 8 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 10 (or when Week 8 labs available)
Week 12 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 14 (or when Week 12 labs available)
Week 16 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 18 (or when Week 16 labs available)
Week 20 (at home or the study site)	Potential GC dose increase (if needed) at approximately Week 22 (or when Week 20 labs available) to maintain androstenedione control

GC=glucocorticoid

At all visits, if A4 is >120% of baseline and >ULN, increase glucocorticoid dose as appropriate in order to maintain A4 control.

For the Week 28 visit, subjects should hold their morning glucocorticoid and study drug dose until after the predose blood samples are collected, with dosing to occur between approximately 0800 and 0830 hours with breakfast. For subjects ≥6 years of age with a body weight ≥20 kg, another blood sample will be collected approximately 3 hours after the morning glucocorticoid and study drug dose. For all subjects, salivary samples will be collected over the course of the day: at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid and study drug dosing and 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of glucocorticoid (if subject is not taking evening glucocorticoid dose, then prior to bedtime). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose salivary sample is collected.

7.3. Open-Label Treatment Period (Week 28 to Week 52)

From the evening of the Week 28 visit (after all Week 28 assessments have been performed) until the morning of the Week 52 visit, all subjects will receive active study drug based on their Week 28 weight (crinecerfont; 25 mg bid via oral solution for subjects 10 to <20 kg, 50 mg bid via oral solution for subjects 20 to <55 kg, or 100 mg bid via oral capsules for subjects ≥55 kg) with breakfast and evening meals. Subjects and investigators will remain blinded to subjects' randomized treatment group assignment during the entire study. From Week 28 until Week 32, subjects should maintain a stable glucocorticoid regimen to the extent possible, except for stress dosing if needed for illness or other significant physical stress. A blood sample will be collected at Week 32 (at home or the study site).

For subjects who are on >11 mg/m^2/day glucocorticoid dose (in hydrocortisone dose equivalents adjusted for BSA [based on weight and height at Week 28]) at Week 32, further adjustments in glucocorticoid dose should be made following guidelines similar to that used during the placebo-controlled period with the goal to reach a target dose of 8 to 10 mg/m^2/day in hydrocortisone dose equivalents adjusted for BSA at Week 52, while A4 is controlled. The calculation of glucocorticoid dose in hydrocortisone equivalents adjusted for BSA at Week 52 will be based on height and weight measurement at Week 52. BSA will be updated at Week 40 if height measurement is obtained at Week 40.

The first glucocorticoid dose adjustment step during this period (if done) should be guided by the serum A4 change at Week 32 (compared with Week 28), after the subject has been on open-label active study drug as well as stable glucocorticoid regimen (to the extent possible) for 4 weeks. A suggested guideline is provided in Table 5 but the exact amount adjusted may differ from this guideline based on practical issues considered in clinical practice related to available dosage strengths. The investigator should contact the subject/guardian once the Week 32 lab results are available in order to provide guidance on the amount of the first glucocorticoid dose adjustment (if needed) during the open-label treatment period.

Table 5: Guide for Glucocorticoid Dose Adjustment During the Open-Label Treatment Period

Percent Change from Week 28 in Serum Androstenedione	Androstenedione Level	Glucocorticoid Dose Adjustment
Any increase	>ULN	Consider whether glucocorticoid dose needs to be increased
Any increase	≤ULN	Maintain current glucocorticoid dose
No change[a]	Any	Maintain current glucocorticoid dose
Decrease of ≤20%	Any	1 to 2 mg/m^2/day glucocorticoid dose reduction
Decrease of >20% to ≤40%	Any	2 to 3 mg/m^2/day glucocorticoid dose reduction
Decrease of >40%	Any	3 to 4 mg/m^2/day glucocorticoid dose reduction

ULN =upper limit of normal
[a] Within reasonable variability in the opinion of the investigator.

If the glucocorticoid dose is modified at approximately Week 34, a follow-up blood test (with salivary sample collection) should be arranged approximately 2 weeks later at Week 36 (at home or the study site).

If needed, subsequent glucocorticoid dose adjustments should occur at approximately Week 38 and Week 42 (or when lab results are available) with follow-up blood and salivary tests at Week 40 (at home or the study site) and Week 44 (at home or the study site, if the glucocorticoid dose was previously modified during the open-label treatment period) (Table 6). The target amount of glucocorticoid dose reduction at each step is approximately 1 to 4 mg/m^2/day but should be guided by the A4 level at the preceding blood test as well as practical issues considered in clinical practice related to available dosage strengths.

Table 6: Schedule for Blood Tests and Potential Glucocorticoid Dose Adjustments During the Open-Label Treatment Period

Blood Test (Including Androstenedione)	Glucocorticoid Dose Adjustment Step
Week 36 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 38 (or when Week 36 androstenedione result is available)
Week 40 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 42 (or when Week 40 androstenedione result is available)
Week 44 (at home or the study site)	Potential GC dose increase (if needed) at approximately Week 46 (or when Week 44 labs available) to maintain androstenedione control

GC=glucocorticoid; ULN=upper limit of normal

At all visits, if A4 is >120% of baseline and >ULN, increase glucocorticoid dose as appropriate in order to maintain A4 control.

For the Week 52 visit, subjects should hold their morning glucocorticoid and study drug dose until after the predose blood samples are collected, with dosing to occur between approximately 0800 and 0830 hours with breakfast. For subjects ≥6 years of age with a body weight ≥20 kg, another blood sample will be collected approximately 3 hours after the morning glucocorticoid and study drug dose. For all subjects, salivary samples will be collected over the course of the day: at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid and study drug dosing and 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of glucocorticoid (if subject is not taking evening glucocorticoid dose, then prior to bedtime). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose salivary sample is collected.

7.4. Open-Label Extension for Continued Crinecerfont Access (Month 12 [Week 52] Onwards)

At Month 12 (Week 52), the subject's parent(s) or legal guardian(s) (or the subject, if the subject has reached the age of majority) will review applicable portions of the informed consent form (ICF) and the subject will review applicable portions of the assent form (if applicable) and confirm whether the subject will participate in the optional OLE.

During the OLE, subjects will continue to receive crinecerfont at the appropriate dose based on their body weight at each study visit (25 mg bid if weight is 10 to <20 kg, 50 mg bid if weight is 20 to <55 kg, 100 mg bid if weight is ≥55 kg), unless the subject has inadequate efficacy (in the opinion of the investigator), in which case the crinecerfont dose can be increased by doubling the evening dose. Dose can be increased for inadequate efficacy once at the specified weight-based dose (eg, 50 mg BID can be increased to 50 mg qam and 100 mg qpm) but not further unless the subject crosses into the next weight category. If the investigator assesses the subject as having inadequate efficacy and in addition the subject has crossed into the next weight category, the crinecerfont dose should be increased first based on weight (not doubling the evening dose), and then dose adjustment for inadequate efficacy should be assessed at the next scheduled study visit. If the crinecerfont dose is increased due to inadequate efficacy, a follow-up study visit should be performed approximately 1 month after the dose increase for efficacy, PK, and safety assessments. This follow-up study visit is not required for subjects who increase their dose due to crossing into the next weight category. Changes to the crinecerfont dose (whether based on crossing into the next weight category or based on inadequate efficacy) should generally only be made at scheduled study visits. Further guidance on changes to crinecerfont dosing in the OLE is provided in Appendix B.

At Month 12, subjects taking crinecerfont 50 mg bid or higher may elect to switch the crinecerfont formulation (oral solution or capsule) based on preference, eg, if the subject was receiving crinecerfont 50 mg bid oral solution from Week 28 to Month 12 but prefers the capsule, they could switch to 50 mg bid capsule if remaining in the same weight category. Once this formulation preference is established at Month 12, the formulation should remain the same for the rest of the OLE (unless there is a tolerability issue, in which case the subject can revert back to the previous formulation, ideally within approximately 1 month).

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 investigator should contact the subject/guardian (within 2 weeks) to assess how the subject is tolerating the glucocorticoid dose reduction. 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.

Starting at Month 12, study visits during the OLE will occur every 6 months. At each OLE study visit (including visits performed approximately 1 month after a dose increase for inadequate efficacy), subjects should hold their morning glucocorticoid and study drug dose until after the predose blood samples are collected, with dosing to occur between approximately 0800 and 0830 hours with breakfast. At Month 24 and every 12 months thereafter, for subjects ≥6 years of age with a body weight ≥20 kg, another blood sample will be collected approximately 3 hours after the morning glucocorticoid and crinecerfont dose. In addition, for all subjects, salivary samples will be collected over the course of the day at Month 24, every 12 months thereafter, and at the early termination visit: at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid and study drug dosing and 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of glucocorticoid (if subject is not taking evening glucocorticoid dose, then prior to bedtime). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose salivary sample is collected.

The study will continue, and subjects have the option to remain in the OLE until crinecerfont becomes commercially available, the Sponsor elects to discontinue development of crinecerfont for CAH, or the Sponsor elects to discontinue the study.

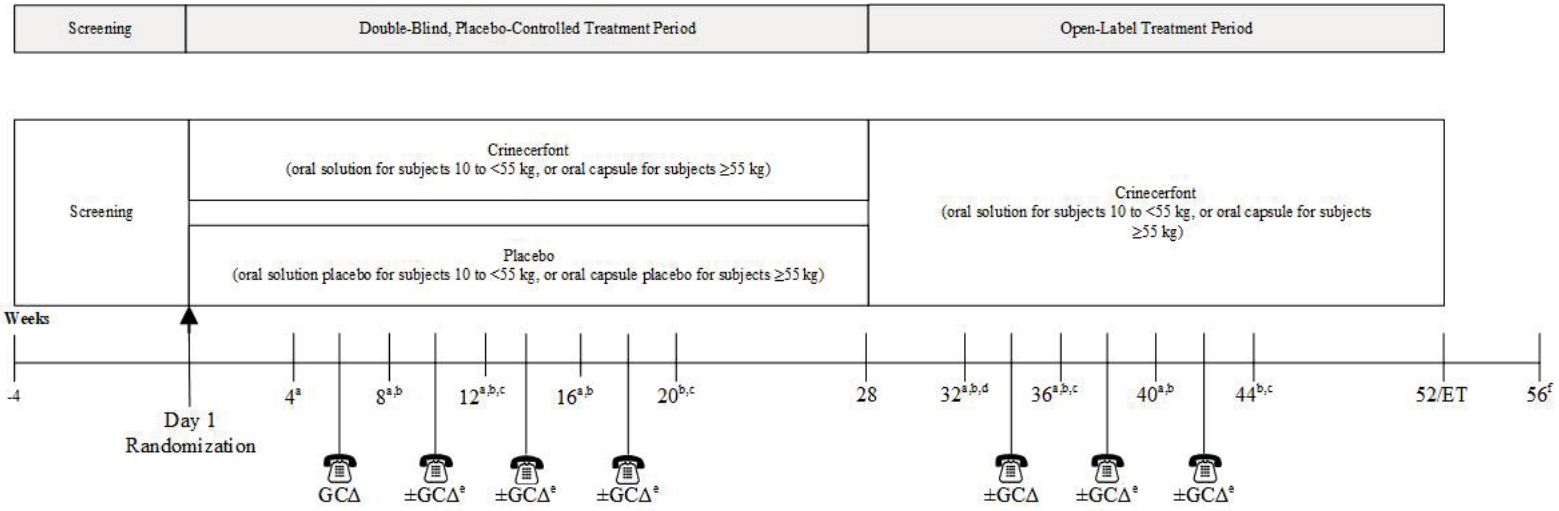
7.5. Follow-up Period

A final posttreatment visit will be conducted approximately 4 weeks after a subject's final dose of study drug. This visit is not required if the subject transitions from the open-label treatment period to the OLE or if the subject transitions from the OLE to commercially available crinecerfont or to another crinecerfont study.

7.6. Study Schematic

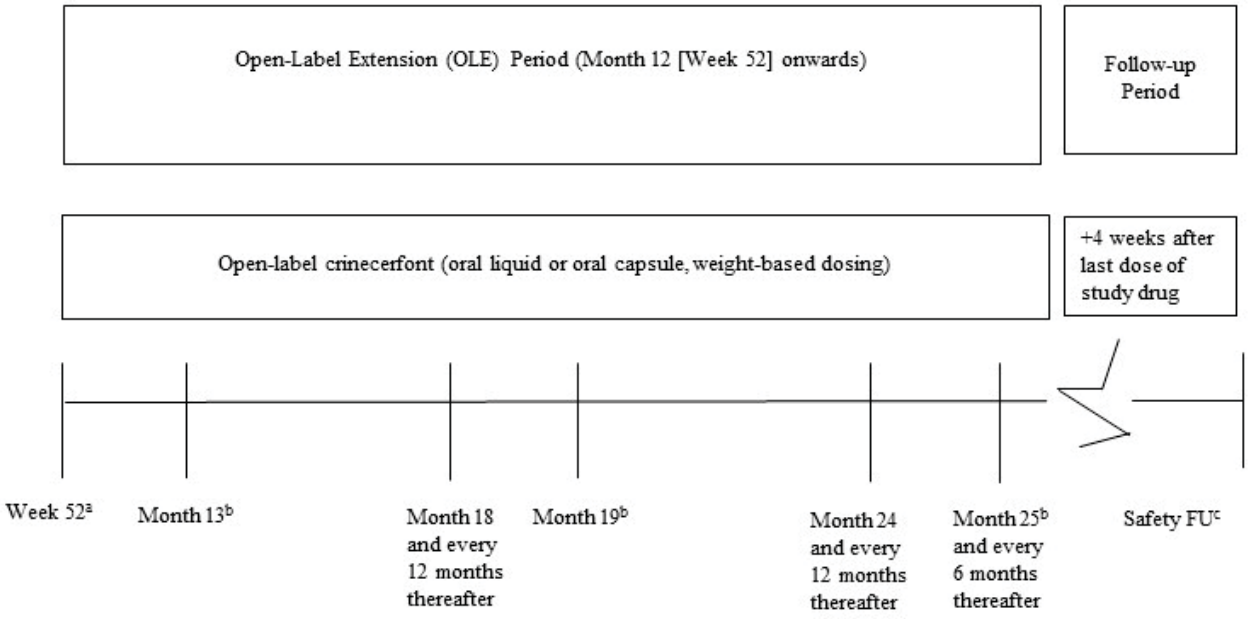
A schematic of the study design for the double-blind, placebo-controlled and open-label treatment periods is shown in Figure 1, and a schematic of the OLE is shown in Figure 2.

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



ET=early termination; GC=glucocorticoid.
[a] If needed, the investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any needed follow-up.
[b] At home or the study site. At Week 16 and Week 40, at home is an option if height is not required.
[c] These visits will occur only if there was any preceding glucocorticoid dose modification during the same treatment period.
[d] Subjects will have further glucocorticoid dose adjustment starting at Week 32 only if their Week 32 glucocorticoid dose is >11 mg/m^2/day.
[e] Glucocorticoid dose adjustments can occur in as few as 1 or up to 3 or 4 steps, depending on the starting and target glucocorticoid doses and the amount of dose adjustment at each step.
[f] Subjects who complete the Week 52 visit and do not enter the OLE will undergo a safety follow-up visit approximately 4 weeks after the last dose of study drug.

Figure 2: Study Design Schematic for Optional Open-Label Extension for Continued Access to Crinecerfont (Month 12/Week 52 Onwards)



bid=twice daily; FU=follow-up; GC=glucocorticoid; ICF=informed consent form; OLE=open-label extension; qam=in the morning; qpm=in the evening

[a] At Month 12 (Week 52) only, the subject's parent(s) or legal guardian(s) (or the subject, if the subject has reached the age of majority) will review applicable portions of the ICF and the subject will review applicable portions of the assent form (if applicable) and confirm whether the subject will participate in the optional OLE At Month 12, subjects taking crinecerfont 50 mg bid or higher may elect to switch the crinecerfont formulation (oral solution or capsule) based on preference.

[b] These visits will only occur if the evening dose was doubled at the preceding visit due to inadequate inefficacy.

[c] This visit is not required if the subject transitions during the OLE to commercially available crinecerfont or to another crinecerfont study.

8. STUDY POPULATION

This study will be conducted in approximately 81 female and male subjects, 2 to 17 years of age at the time of signing the initial informed consent, 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. Have documentation of witnessed written or oral pediatric assent from the subject deemed capable of providing assent, and written informed consent from the subject's parent(s) or legal guardian(s) (or the subject, if the subject has reached the age of majority) in accordance with the governing IRB/IEC and according to local laws and regulations.
2. Be a female or male 2 to 17 years of age with a body weight of at least 10 kg.
3. Have a medically confirmed diagnosis of classic CAH due to 21-hydroxylase deficiency based on standard medically accepted criteria such as elevated 17-OHP level, confirmed CYP21A2 genotype, diagnostic results after cosyntropin stimulation testing.
4. Be on a supraphysiologic glucocorticoid dose regimen defined as >12 mg/m^2/day in hydrocortisone dose equivalents (see Section 9.3.2) that has been stable for at least 1 month prior to screening, is intended for chronic use, and consists ONLY of 1 or more of the following orally administered glucocorticoids: hydrocortisone, prednisone, prednisolone, or methylprednisolone. Subjects must be receiving a morning dose of glucocorticoid.
5. Have an A4 level (prior to the morning glucocorticoid dose) greater than the midpoint of the reference range, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5).
6. Have a 17-OHP level (prior to the morning glucocorticoid dose) >2 × ULN according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5).
7. If treated with fludrocortisone, dose should be stable for at least 1 month prior to screening. Regardless of fludrocortisone treatment, upright plasma renin activity (PRA) (in the absence of medications that confound interpretation of PRA) during screening should be <3 × ULN and >lower limit of normal on the subject's usual sodium intake (if PRA >2 × ULN and <3 × ULN, subject must have normal age-specific systolic blood pressure and heart rate and serum potassium <ULN [Harman et al., 2011]).
8. Female subjects of childbearing potential with fertile male partners must either be completely abstinent from sexual intercourse (periodic abstinence is not acceptable) or 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 of childbearing potential is defined as a female capable of becoming pregnant, which includes subjects who have had their first menstrual cycle (ie, menarche) and are not surgically sterile (ie,

bilateral oophorectomy, hysterectomy, or bilateral tubal ligation for at least 3 months prior to screening).

Acceptable methods of contraception are listed in Section 9.10.1.

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 besides classic CAH due to 21-hydroxylase deficiency requiring chronic daily therapy with oral glucocorticoids.
3. Are 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.
4. 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.
5. Have a history of malignancy, unless successfully treated with curative intent and considered to be cured.
6. 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).
7. Have a known sensitivity (ie, hypersensitivity) or allergy to any corticotropin-releasing hormone receptor antagonist or any component of the study drug.
8. Have evidence of chronic renal or liver disease based on any of these screening laboratory test abnormalities:
   - Estimated glomerular filtration rate <60 mL/min/1.73 m^2.
   - Aspartate aminotransferase (AST) >2 × ULN.
   - Alanine aminotransferase (ALT) >2 × ULN.
   - Total bilirubin >1.5 × ULN unless due to a documented diagnosis of Gilbert's syndrome.
9. Have any of the following hematologic abnormalities at screening:
   - Hemoglobin <10 g/dL (age <6 years) or <11 g/dL (age ≥6 years).
   - White blood cell (WBC) count <4.0 × $10^3/mm^3$.
   - Platelet count <100,000/mm^3.

- Absolute neutrophil count <1.0 × 10^3/mm^3.

10. 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) >1.4, unless the subject is on anticoagulant treatment that affects INR.
11. Have serum sodium <130 mmol/L.
12. Used any active investigational drug within 30 days or 5 half-lives (whichever is longer) before screening, or plans to use an investigational drug (other than the study drug) during the study.
13. Are using any excluded concomitant medication (refer to Section 9.10) and cannot discontinue use of these medications for the duration of the study.
14. Have current substance dependence or substance or alcohol abuse (drugs including controlled substance or nonprescribed use of prescription drugs; nicotine and caffeine dependence are not exclusionary).
15. Have a significant risk of suicidal or violent behavior. Only for subjects ≥6 years of age: 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 lifetime history of suicidal behavior based on the C-SSRS should be excluded.
16. Have had a blood loss ≥3% of total blood volume (based on 75 mL per kg body weight) 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 (eg, ongoing and persistent noncompliance with glucocorticoid therapy).

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 pubertal stage (Tanner breast or genital stage 1 or 2 versus 3, 4 or 5) and sex (see Section 9.7.5.1 for further detail on Tanner staging).

9. STUDY EVALUATIONS

9.1. Schedule of Assessments

A schedule of assessments for the screening period; the double-blind, placebo-controlled treatment period; and the open-label treatment period is shown in Table 7, and a schedule of assessments for the OLE is shown in Table 8.

Prior to any study-related procedures, parental or legal guardian (or subject, if the subject has reached the age of majority) informed consent with signed and witnessed study subject assent will be obtained (which may be done remotely, if allowed and remote consenting procedures are in place), as required by the governing IRB or ethics committee and according to local laws and regulations. At Week 52, the subject's parent(s) or legal guardian(s) (or the subject, if the subject has reached the age of majority) will review applicable portions of the ICF and the subject will review applicable portions of the assent form (if applicable) and confirm whether the subject will participate in the optional OLE for continued access to crinecerfont (Table 8). 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.

All assessments during the core study as well as the OLE that are performed based on the subject's age should be based on the age at time of initial informed consent, unless otherwise specified.

Table 7: Schedule of Assessments – Double-Blind Placebo-Controlled and Open-Label Treatment Periods

Assessment	Screening Period[a,b]	Double-Blind, Placebo-Controlled Treatment Period[a]							Open-Label Treatment Period[a]					Follow-up Period for Subjects Not Entering the OLE[a]
	Week -4 to Day -1	Day 1 (Baseline)	Week 4	Week 8[b]	Week 12[b,c]	Week 16[b]	Week 20[b,c]	Week 28	Week 32[b,d]	Week 36[b,c]	Week 40[b]	Week 44[b,c]	Week 52/ ET	Week 56[e]
Informed consent/assent	X													
Inclusion/exclusion criteria	X	Update												
Medical history	X	Update												
TSH and free T4	X (TSH only)	X						X					X	
UDS[f]	X													
Physical exam	X	X						X					X	
Tanner stage[g]	X	X				X		X			X		X	
Vital signs, height, weight[h]	X	X	X			X		X			X		X	X
Hematology/coagulation	X	X				X		X			X		X	X
Chemistry, cortisol	X	X		X	X	X		X	X	X	X		X	X
Urinalysis	X	X						X					X	X
CYP21A2 genotyping			X											
Pregnancy test[i]	X (s)	X (u)	X (u)			X (u)		X (u)			X (u)		X (u)	X (u)
Serial blood sampling (hormone)[j]		X	X											
PK sample(s) incl serial[k]			X			X		X			X		X	
Salivary samples incl serial[l]		X	X	X	X	X	X	X	X	X	X	X	X	
17-OHP, A4, ACTH[m]	X			X	X	X	X	X	X	X	X	X	X	X
Potential GC dose adjustment[n]			X	X	X	X	X		X	X	X	X		
LH, FSH, testosterone, PRA	X	X				X		X			X		X	
Fasting lipids, HOMA-IR		X						X					X	
Bone age[n]		X						X					X	
Testicular ultrasound[o]		X						X					X	
EQ-5D[p]		X						X					X	
PedsQL[q]		X						X					X	
PedsQL Family Impact		X						X					X	
BPRS-c[r]	X	X						X					X	
C-SSRS[s]	X	X	X			X		X			X		X	X
Hirsutism[t] and Acne Scales		X						X					X	
Menstrual Questionnaire[u]	X	X	X			X		X			X		X	X
Palatability/ease of admin[v]			X					X					X	
6- or 12-lead ECG	X	X	X					X					X	X
Dispense study drug		X	X			X		X			X			
Study drug accountability[w]			X			X		X			X		X	
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior & concomitant meds	X	X	X			X		X			X		X	X

17-OHP=17-hydroxyprogesterone; A4=androstenedione; ACTH= adrenocorticotropic hormone; admin=administration; AE=adverse event; BPRS-c=Brief Psychiatric Rating Scale, Children's Version; C-SSRS=Columbia-Suicide Severity Rating Scale; CYP=cytochrome P450; ECG=electrocardiogram; ET=early termination; FSH=follicle-stimulating hormone; GC=glucocorticoid; HOMA-IR=homeostatic model assessment of insulin resistance; incl=including; LH=luteinizing hormone; OLE=open-label extension; PedsQL=Pediatric Quality of Life Instrument; PK=pharmacokinetics; PRA=plasma renin activity; s=serum; T4=thyroxine; TSH=thyroid-stimulating hormone; u=urine; UDS=urine drug screen.

[a] The screening period can be extended by up to 4 weeks after discussion with and approval of the Medical Monitor to allow for delayed screening laboratory results that are needed to determine eligibility or to accommodate other extenuating logistical issues, such as scheduling. The Week 4 visit will have a visit window of ±5 days, and subsequent visits through Week 52 will have a visit window of ±7 days. The Week 56 visit (if applicable) visit has a visit window of +7 days. All Week 28 assessments should be completed before a subject begins open-label treatment. Not all assessments must be conducted on the same day, but all assessments for a given visit must be completed within the visit window. If a subject's GC regimen is adjusted due to stress dosing, the subject should resume their GC dosing regimen for at least 3 days before their next scheduled lab test if the duration of stress dosing is 3 days or less, and for at least 7 days before their next scheduled lab test if the duration of stress dosing is ≥4 days (this 3- or 7-day window supersedes all other visit windows).

[b] At home or the study site. At Week 16 and Week 40, at home is an option if height is not required. During the screening period, blood and urine collection may be arranged at home.

[c] Only if a preceding GC dose adjustment occurred.

[d] Subjects will have further GC adjustment starting at Week 32 only if their Week 32 GC dose is >11 mg/m^2/day.

[e] For subjects who discontinue the study prior to Week 52, assessments will be performed at the ET visit and at the safety follow-up visit, consisting of the same procedures as shown for Week 56 in the schedule of assessments. A safety follow-up visit is not required if the last dose of study drug was at least 4 weeks prior to the ET visit. Subjects who complete the Week 52 visit and elect to not enter the OLE will undergo a safety follow-up visit approximately 4 weeks after last dose of study drug.

[f] Only for subjects age ≥12 years of age.

[g] Tanner stage at screening and Day 1. Historical assessment of Tanner staging is acceptable if Tanner stage 5 has been previously documented. Tanner staging at subsequent visits is required only if baseline Tanner stage <5. In addition, subjects with Tanner stage 4 at baseline do not need to undergo Tanner staging at Week 16 or Week 40.

[h] Measure blood pressure 3 times, in up to 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Measure weight with subjects not wearing shoes or outerwear (eg, jackets or coats). Measure height (in subjects not wearing shoes) as the average of 3 to 6 measurements using a stadiometer (or length board) (Section 9.3.3). Height not required at Week 4 or Week 56 (all subjects) or at Week 16 and Week 40 if growth <2.5 cm in past year, complete fusion of epiphyses on hand/wrist radiograph, or more than 2 years past menarche (females).

[i] Only for females of childbearing potential. Serum pregnancy testing at screening, urine pregnancy tests at other visits.

[j] Blood samples for A4, 17-OHP, and ACTH will be collected:

- For subjects who are ≥6 years of age with a body weight ≥20 kg: On Day 1 and Week 4 approximately 15 minutes before and just prior to dosing with the morning GC and (Week 4) study drug between approximately 0800 and 0830 hours and at 2, 3, 4, and 6 hours after dosing. Any midday GC dose the subject is receiving should be taken after blood is sampled 6 hours after dosing.
- For subjects who are ≥6 years of age with body weight ≥20 to <30 kg: only a single sample for ACTH will be collected, which will be the sample just prior to the morning GC dose.
- For subjects who are <6 years of age or with a body weight <20 kg: collect a blood sample prior to dosing with the morning GC, (if applicable) fludrocortisone, and (Week 4) study drug, with dosing between approximately 0800 and 0830 hours.

All subjects should take their GC dose the night before prior to 2100 hours.

[k] For all subjects, a blood sample for PK prior to the morning study dose will be collected at Weeks 4, 16, 28, 40, and 52/ET, if ET occurs prior to Week 52. At Week 4: for subjects who are ≥6 years of age with a body weight ≥30 kg, blood samples for PK will also be collected approximately 2, 3, 4, and 6 hours after dosing.

[l] Salivary samples for adrenal androgens and precursors will be collected:

- Day 1 and Weeks 4, 28, and 52/ET: at approximately 0600 hours, at approximately 0800 hours prior to dosing with morning GC and (after Day 1) study drug and at approximately 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of GC; if subject is not on an evening GC dose, then prior to bedtime. Any midday GC dose that the subject is receiving should be taken after the salivary sample collection 6 hours after dosing.
- Weeks 8, 12, 16, 20, 32, 36, 40, 44, and 56: prior to morning GC dose at approximately the same time as the blood sample. If a blood sample is not obtained at a visit (eg, because no GC dose adjustment was required), a salivary sample does not need to be obtained.

[m] Subjects should take their GC dose the night before prior to 2100 hours and hold their morning dose of GC, fludrocortisone (if applicable), and study drug (except screening) until after predose blood sample collection. The blood sample collection will include 17-OHP and A4 at all visits, and will also include ACTH at Weeks 16, 28, 40, 52/ET, and 56. Morning dosing should occur between approximately 0800 and 0830 hours with breakfast. At Week 28 and Week 52/ET, another blood sample will be collected at 3 hours after dosing for subjects ≥6 years of age with body weight ≥20 kg.

[n] Only in females with the most recent prior bone age <14 years and males with the most recent prior bone age <16 years. Bone age assessment is not required at the ET visit if the subject had a bone age assessment within 3 months prior.

[o] Only in male subjects. Week 28 and Week 52/ET ultrasound only if testicular adrenal rest tumor(s) demonstrated on Day 1. Testicular ultrasound is not required at the ET visit if the subject had a testicular ultrasound within 3 months prior.

[p] EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for age 16 years and older.

[q] PedsQL Toddler Version for age 2 to 4 years, Young Child Version for age 5 to 7 years, Child Version for age 8 to 12 years, Adolescent Version for age 13 to 17 years.

[r] Only for subjects ≥3 years of age.

[s] Only for subjects ≥6 years of age. Baseline/Screening version used at screening, and Since Last Visit version at subsequent visits.

[t] Hirsutism scale only for females.

[u] Menstrual Cycle Questionnaire only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives.

[v] Palatability will be assessed for subjects ≥6 years of age, and ease of administration will be assessed by caregivers of subjects <6 years of age. The palatability/ease of administration assessment should be administered within approximately 15 minutes after study drug dosing.

[w] Subjects will return all unused study drug and packaging, and a compliance check will be performed.

Table 8: Schedule of Assessments – Open-Label Extension (Month 12 [Week 52] Onwards)

Assessment	OLE[a]							OLE Follow-up Period[a]
	Month 12 (Week 52) [b,c]	Month 13 (only if evening crinecerfont dose doubled the previous month)	Month 18 and Every 12 Months Thereafter[c]	Month 19 (only if evening crinecerfont dose doubled the previous month)	Month 24 and Every 12 Months Thereafter[c]	Month 25 and Every 6 Months Thereafter (only if evening crinecerfont dose doubled the previous month)	OLE ET	Final Study Visit (~4 weeks after last dose of study drug)[d]
Informed consent/assent[e]	X							
Physical exam		X		X	X	X	X	
TSH and free T4					X			
Tanner stage[f]			X		X		X	
Vital signs, height, weight[g]		X	X	X	X	X	X	X
6- or 12-lead ECG		X		X		X	X	
Hematology/coagulation			X		X		X	X
Chemistry, cortisol		X	X	X	X	X	X	X
Urinalysis					X		X	X
Urine pregnancy test[h]					X		X	X
PK sample(s)[i]		X	X[j]	X	X[j]	X		
Salivary samples incl serial[k]					X		X	
17-OHP, A4, ACTH		X	X	X	X[l]	X	X	X
LH, FSH, testosterone, PRA		X	X	X	X	X	X	
Fasting lipids, HOMA-IR			X		X		X	
Bone age[m]			X		X		X	
Testicular ultrasound[n]	X[n]				X		X	
EQ-5D[o]					X		X	
BPRS-c[p]					X		X	
C-SSRS[q]			X		X		X	X
Hirsutism[r] and Acne Scales			X		X		X	
Menstrual Questionnaire[s]			X		X		X	X
Dispense study drug[t]	X		X		X			
Study drug accountability[u]			X		X		X	
AE monitoring		X	X	X	X	X	X	X
Prior & concomitant medications		X	X	X	X	X	X	X

17-OHP=17-hydroxyprogesterone; A4=androstenedione; ACTH= adrenocorticotropic hormone; AE=adverse event; BPRS-c=Brief Psychiatric Rating Scale for Children; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; FSH=follicle-stimulating hormone; GC=glucocorticoid; HOMA-IR=homeostatic model assessment of insulin resistance; ICF=informed consent form; LH=luteinizing hormone; OLE=open-label extension; PK=pharmacokinetics; PRA=plasma renin activity; T4=thyroxine; TART=testicular adrenal rest tumor; TSH=thyroid-stimulating hormone.

[a] The Month 12 (Week 52) will have a visit window of ±7 days. Each 6-month visit (Month 12, 24, 30, 36, etc)er will have a visit window of ±14 days. The visit 4 weeks following doubling of the evening dose will have a visit window of ±7 days relative to the visit at which the dose was increased; and the final study visit will have a visit window of +14 days.

[b] The Month 12 (Week 52) visit in the OLE is the same as the Week 52/ET visit in the open-label treatment period. Please refer to Table 7 for the Week 52 assessments.

[c] Within 2 weeks after any GC dose reduction, the investigator will contact the subject's parent(s)/guardians 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] This visit is not required if the last dose of study drug was at least 4 weeks prior to the early termination visit, or if the subject transitions during the OLE to commercially available crinecerfont or to another crinecerfont study.

[e] At the Month 12 (Week 52) visit, the subject's parent(s) or legal guardian(s) (or the subject, if the subject has reached the age of majority) will review applicable portions of the ICF and the subject will review applicable portions of the assent form (if applicable) to confirm the subject's participation in the optional OLE. Subjects should also complete all Month 12 (Week 52) assessments from the open-label treatment period (see Table 7).

[f] Subjects who have been assessed as Tanner stage 5 at any visit are not required to undergo assessment of Tanner stage at subsequent visits.

[g] Measure blood pressure 3 times, in up to 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Measure weight with subjects not wearing shoes or outerwear (eg, jackets or coats). Measure height (in subjects not wearing shoes) as the average of 3 to 6 measurements using a stadiometer (or length board) (Section 9.7.3). Height should be assessed at each 6-month visit.

[h] Only for females of childbearing potential.

[i] For all subjects, a blood sample for PK prior to the morning study dose will be collected at Week 52 visit as part of the open-label treatment period (see Table 7).

[j] Only for subjects who had their evening dose of crinecerfont doubled at the previous 6-month visit. Further PK samples will not be required during the OLE after the PK samples obtained 1 month and 6 months following a dose increase for inadequate efficacy.

[k] For all subjects at Month 24 and every 12 months, and at ET visit, salivary samples for adrenal androgens and precursors will be collected at approximately 0600 hours, at approximately 0800 hours prior to dosing with morning GC and study drug, approximately 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of GC; if subject is not on an evening GC dose, then prior to bedtime. Salivary samples at approximately 0800 hours prior to and 3 and 6 hours after the morning GC dose should occur at approximately the same time as the corresponding blood samples (as applicable). Any midday GC dose that the subject is receiving should be taken after the 6-hour postdose blood and salivary samples are collected.

[l] At these visits, subjects should take their GC dose the night before prior to 2100 hours and hold their morning dose of GC, fludrocortisone (if applicable), and study drug until after predose blood sample collection. Dosing with the morning GC, fludrocortisone (if applicable), and study drug should occur between approximately 0800 and 0830 hours with breakfast. At Month 24 and every 12 months thereafter, and at ET, another blood sample will be collected at 3 hours after dosing for subjects ≥6 years of age with body weight ≥20 kg.

[m] Only in females with the most recent prior bone age <14 years and males with the most recent prior bone age <16 years. Bone age assessment is not required at the early termination visit if the subject had a bone age assessment within 3 months prior.

[n] All male subjects continuing in the OLE will have a testicular ultrasound at Week 52, including subjects who are not required to have a Week 52 ultrasound as part of the core study. An ultrasound will be performed at Month 24 and every 12 months thereafter only if the Week 52 ultrasound demonstrates the presence of TARTs. All male subjects will have a testicular ultrasound at the early termination visit except for subjects who have had a testicular ultrasound within 3 months prior to the early termination visit.

[o] EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for age ≥16 years. Subjects entering the OLE will have age recalculated and use the appropriate EQ-5D instrument based on age of entry into the OLE.

[p] Only for subjects ≥3 years of age. In the OLE, the BPRS-c will continue to be administered to subjects who are ≥18 years of age.

[q] Only for subjects ≥6 years of age.

[r] Hirsutism scale only for females.

[s] Menstrual Cycle Questionnaire only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives.

[t] Study drug will be dispensed every 3 months.

[u] Subjects will return all unused study drug, and a compliance check will be performed by counting the capsules returned, at each study visit except for the additional visits that occur 1 month after doubling of the evening dose for inadequate efficacy.

9.2. Screening and Baseline Assessments

Prior to any study-related procedures, parental or legal guardian informed consent with signed and witnessed study subject assent will be obtained (which may be done remotely, if allowed and remote consenting procedures are in place), as required by the governing IRB or ethics committee and according to local laws and regulations. Subjects will undergo screening for up to 4 weeks (Weeks -4 to Day -1) to determine eligibility. The screening period can be extended by up to 4 weeks after discussion with and approval of the Medical Monitor to allow for delayed screening laboratory results that are needed to determine eligibility or to accommodate other extenuating logistical issues, such as scheduling. Prior to blood sample collection during screening, subjects will be asked to take their evening glucocorticoid dose the night before prior to 2100 hours and hold their morning dose of glucocorticoid and fludrocortisone (if applicable), with dosing to occur between approximately 0800 and 0830 hours. During the screening period, blood sample collection may be performed at home. 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.

A TSH level will be measured at screening.

Estimated glomerular filtration rate will be calculated from serum creatinine (using bedside Schwartz formula) at screening.

A urine sample will be tested for amphetamines, barbiturates, benzodiazepines, cocaine, phencyclidine, and opiates at screening (only for subjects ≥12 years of age).

9.3. Efficacy Assessments

9.3.1. Hormone Measurements

9.3.1.1. Serum or Plasma Hormone Measurements

For subjects who are ≥6 years of age with a body weight ≥20 kg: blood samples will be collected on Day 1 and Week 4 approximately 15 minutes before and immediately prior to dosing with the morning glucocorticoid and (if applicable) fludrocortisone (Day 1 and Week 4), and study drug (Week 4) (with dosing to occur between approximately 0800 and 0830 hours with breakfast) and at 2, 3, 4, and 6 hours after dosing for A4, 17-OHP, and ACTH (for subjects with body weight ≥20 to <30 kg, only a single sample for ACTH will be collected, which will be the sample just prior to the morning glucocorticoid dose). LH, FSH, testosterone, and PRA will be measured in a predose sample. Any midday glucocorticoid dose that the subject is receiving should be taken after the blood sample collection 6 hours after dosing. Subjects who are <6 years of age or with a body weight <20 kg will have a blood sample collected for A4, 17-OHP, ACTH, LH, FSH, testosterone, and PRA prior to dosing with the morning glucocorticoid and (if applicable) fludrocortisone (Day 1 and Week 4) and study drug (Week 4) (with dosing to occur between approximately 0800 and 0830 hours with breakfast). All subjects should take their glucocorticoid dose the night before prior to 2100 hours.

At all study visits after Week 4, all subjects should take their evening glucocorticoid dose the night before prior to 2100 hours and hold their morning glucocorticoid, fludrocortisone (if applicable), and study drug dose until after blood sample collection for hormone measurements,

with dosing to occur between approximately 0800 and 0830 hours with breakfast. At Week 28, Month 12 (Week 52), Month 24 and every 12 months thereafter, and early termination, another blood sample will be collected for A4, 17-OHP, and ACTH approximately 3 hours after the morning glucocorticoid, fludrocortisone (if applicable), and study drug dose for subjects ≥6 years of age with body weight ≥20 kg.

Hormones to be measured include A4, 17-OHP, cortisol, ACTH, LH, FSH, testosterone, and PRA as specified in Table 7 and Table 8. For reference ranges that depend on pubertal stage, the breast (female) or genital (male) stage should be used (see Section 9.7.5.1). All blood samples will be processed and stored according to the procedures specified in the laboratory manual.

If needed, an appropriate topical anesthetic or numbing device could be used prior to blood sample collection. Blood samples should be obtained by trained personnel who are experienced in pediatric venipuncture skills and appropriate management of pediatric patients to reduce any potential stress associated with blood draws.

9.3.1.2. Salivary Hormone Measurements

Salivary samples for adrenal steroid measurements (including A4, 17-OHP, testosterone, cortisol) will be collected for all subjects:

- Day 1, Weeks 4, 28, and 52, Month 24 and every 12 months thereafter, and early termination: at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid and (Weeks 4, 28, and 52 only) study drug dosing and 3 and 6 hours after dosing (any midday glucocorticoid dose that the subject is receiving should be taken after the salivary sample collection 6 hours after dosing), and within 30 minutes prior to the evening dose of glucocorticoid; if subject is not on an evening glucocorticoid dose, then prior to bedtime.
- Weeks 8, 12, 16, 20, 32, 36, 40, 44, and 56: prior to morning glucocorticoid dose at approximately the same time as the blood sample. If a blood sample is not obtained at a visit (eg, because no glucocorticoid dose adjustment was required), a salivary sample does not need to be obtained.

Subjects will be provided training and all materials needed to collect the salivary samples at home. This will include instructions on proper storage and transfer of the samples.

9.3.2. Glucocorticoid Dosing and Dose Reduction

Each subject will record their daily glucocorticoid regimen in the electronic diary (eDiary) beginning at the screening visit until Week 52 (or Week 56 if subject does not enter OLE), including specific type of glucocorticoid and all doses taken each day for their usual regimen as well as any additional or stress dosing. The usual daily regimen will be converted to hydrocortisone dose equivalents (mg/m^2/day; with a hydrocortisone equivalency ratio of 4 for methylprednisolone, prednisolone, and prednisone) adjusted for BSA for the purpose of analysis.

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 stress dosing (Section 9.7.2). If a subject's glucocorticoid regimen is adjusted due to stress dosing, the subject should resume their glucocorticoid dosing regimen for at least 3 days before their next scheduled lab test if the duration of stress dosing is 3 days or less, and for at least 7 days before their next

scheduled lab test if the duration of stress dosing is ≥4 days (of note, this 3- or 7-day window supersedes all other visit windows).

9.3.2.1. Glucocorticoid Dose Adjustment During Placebo-Controlled Period

From Day 1 until Week 4, subjects should maintain a stable glucocorticoid regimen to the extent possible, except for stress dosing if needed for illness or other significant physical stress, in order to assess the direct effect of study drug on adrenal androgen and precursor levels.

From Week 4 until Week 28, the subject's glucocorticoid dose should be adjusted according to their A4 levels, with the goal to reach a target dose of 8 to 10 mg/m^2/day (in hydrocortisone dose equivalents adjusted for BSA) at Week 28, while A4 is controlled. The calculation of glucocorticoid dose in hydrocortisone equivalents adjusted for BSA at Day 1 and Week 28 will be based on height and weight measurement at Day 1 and Week 28, respectively. BSA will be updated at Week 16 if height measurement is obtained at Week 16.

Glucocorticoid dose adjustments can occur in as few as 1 or up to 4 steps, depending on the starting and target glucocorticoid doses and the amount of dose adjustment at each step. Reductions in the glucocorticoid dose should follow the guideline of first reducing the most nonphysiologic glucocorticoid type and timing. The target glucocorticoid dose should be within the range of 8 to 10 mg/m^2/day while A4 levels are at or below baseline levels and as long as there is no evidence of glucocorticoid insufficiency. The dose could be lower than this range if the investigator considers this appropriate depending on practical issues considered in clinical practice related to available dosage strengths but will not be mandated to be lower than this range. 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. Before any glucocorticoid dose reduction is implemented, the investigator will evaluate the subject for any symptoms suggestive of glucocorticoid insufficiency using a standardized checklist and will arrange for follow-up if needed after the dose reduction.

The first glucocorticoid dose adjustment step at approximately Week 6 (or when the Week 4 lab results are available) should be guided by the change in A4 at Week 4 from baseline. A suggested guideline is provided in Table 9, but the exact amount adjusted may differ from this guideline based on practical issues considered in clinical practice related to available dosage strengths. The investigator should contact the subject's parent(s)/guardians once the Week 4 lab results are available in order to provide guidance on the amount of the first glucocorticoid dose adjustment.

Table 9: Guide for Glucocorticoid Dose Adjustments During the Randomized, Placebo-Controlled Treatment Period

Percent Change From Baseline in Serum Androstenedione	Androstenedione Level	Glucocorticoid Dose Adjustment
Any increase	>ULN	Consider whether glucocorticoid dose needs to be increased
Any increase	≤ULN	Maintain current glucocorticoid dose
No change [a]	Any	Maintain current glucocorticoid dose
Decrease of ≤20%	Any	1 to 2 mg/m^2/day glucocorticoid dose decrease
Decrease of >20% to ≤40%	Any	2 to 3 mg/m^2/day glucocorticoid dose decrease
Decrease of >40%	Any	3 to 4 mg/m^2/day glucocorticoid dose decrease

ULN=upper limit of normal
[a] Within reasonable variability in the opinion of the investigator.

A follow-up blood test (with salivary sample collection) should be arranged approximately 2 weeks later at Week 8 (at home or the study site).

If needed, subsequent glucocorticoid dose adjustment steps should occur when lab results are available (at approximately Week 10, Week 14, and Week 18) with follow-up blood and salivary tests at Week 12 (at home or the study site, if the glucocorticoid dose was previously modified), Week 16 (at home or the study site), and Week 20 (at home or the study site, if the glucocorticoid dose was previously modified) (Table 10). The target amount of glucocorticoid dose reduction at each step is approximately 1 to 4 mg/m^2/day but should be guided by the A4 level at the preceding blood test as well as on practical issues considered in clinical practice related to available dosage strengths.

Table 10: Schedule for Blood Tests and Potential Glucocorticoid Dose Adjustments During the Randomized, Placebo-Controlled Treatment Period

Blood Test (including androstenedione)	Glucocorticoid Dose Adjustment Step
Week 8 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 10 (or when Week 8 labs available)
Week 12 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 14 (or when Week 12 labs available)
Week 16 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 18 (or when Week 16 labs available)
Week 20 (at home or the study site)	Potential GC dose increase (if needed) at approximately Week 22 (or when Week 20 labs available) to maintain androstenedione control

GC=glucocorticoid.

At all visits, if A4 is >120% of baseline and >ULN, increase glucocorticoid dose as appropriate in order to maintain A4 control.

9.3.2.2. Glucocorticoid Dose Adjustment During Open-Label Treatment Period

From Week 28 until Week 32, subjects should maintain a stable glucocorticoid regimen to the extent possible, except for stress dosing if needed for illness or other significant physical stress. A blood sample will be collected at Week 32 (at home or the study site).

For subjects who are on >11 mg/m^2/day glucocorticoid dose at Week 32, further adjustments in glucocorticoid dose should be made following guidelines similar to that used during the placebo-controlled period, with the goal to reach a target dose of 8 to 10 mg/m^2/day in hydrocortisone dose equivalents adjusted for BSA at Week 52, while A4 is controlled. The calculation of glucocorticoid dose in hydrocortisone equivalents adjusted for BSA at Week 52 will be based on height and weight measurement at Week 52. BSA will be updated at Week 40 if height measurement is obtained at Week 40.

The first glucocorticoid dose adjustment step during this period (if done) should be guided by the serum A4 change at Week 32 (compared with Week 28), after the subject has been on open-label active study drug as well as stable glucocorticoid regimen (to the extent possible) for 4 weeks. A suggested guideline is provided in Table 11 but the exact amount adjusted may differ from this guideline based on practical issues considered in clinical practice related to available dosage strengths. The investigator should contact the subject/guardian once the Week 32 lab results are available in order to provide guidance on the amount of the first glucocorticoid dose adjustment (if needed) during the open-label treatment period.

Table 11: Guide for Glucocorticoid Dose Adjustment During the Open-Label Treatment Period

Percent Change from Week 28 in Serum Androstenedione	Androstenedione Level	Glucocorticoid Dose Adjustment
Any increase	>ULN	Consider whether glucocorticoid dose needs to be increased
Any increase	≤ULN	Maintain current glucocorticoid dose
No change[a]	Any	Maintain current glucocorticoid dose
Decrease of ≤20%	Any	1 to 2 mg/m^2/day glucocorticoid dose reduction
Decrease of >20% to ≤40%	Any	2 to 3 mg/m^2/day glucocorticoid dose reduction
Decrease of >40%	Any	3 to 4 mg/m^2/day glucocorticoid dose reduction

ULN=upper limit of normal
[a] Within reasonable variability in the opinion of the investigator.

If the glucocorticoid dose is modified at approximately Week 34, a follow-up blood test (with salivary sample collection) should be arranged approximately 2 weeks later at Week 36 (at home or the study site).

If needed, subsequent glucocorticoid dose adjustments should occur at approximately Week 38 and Week 42 (or when lab results are available) with follow-up blood and salivary tests at Week 40 (at home or the study site) and Week 44 (at home or the study site, if the glucocorticoid dose was previously modified during the open-label treatment period) (Table 12). The target amount of glucocorticoid dose reduction at each step is approximately 1 to 4 mg/m^2/day but should be guided by the A4 level at the preceding blood test as well as practical issues considered in clinical practice related to available dosage strengths.

Table 12: Schedule for Blood Tests and Potential Glucocorticoid Dose Adjustments During the Open-Label Treatment Period

Blood Test (Including Androstenedione)	Glucocorticoid Dose Adjustment Step
Week 36 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 38 (or when Week 36 androstenedione result is available)
Week 40 (at home or the study site)	Potential GC dose adjustment (if needed) at approximately Week 42 (or when Week 40 androstenedione result is available)
Week 44 (at home or the study site)	Potential GC dose increase (if needed) at approximately Week 46 (or when Week 44 labs available) to maintain androstenedione control

GC=glucocorticoid.

At all visits, if A4 is >120% of baseline and >ULN, increase glucocorticoid dose as appropriate in order to maintain A4 control.

9.3.2.3. Glucocorticoid Dose Reduction During Open-Label Extension

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 investigator should contact the subject/subject's parent(s)/guardians (within 2 weeks) to assess how the subject is tolerating the glucocorticoid dose reduction.
- In the setting of inadequate efficacy, 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 (ie, evening crinecerfont dose doubled). 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.

9.3.3. Height and Body Weight

Height will be measured using a wall-mounted stadiometer in a subject without shoes, while instructed to stand tall with feet flat on the floor, heels against the wall, and looking straight forward. Subjects less than 3 years of age may be measured with a length board, but all measurements during the study should be made with the same technique (stadiometer or length board). Measurements should be recorded to the nearest 0.1 cm as the average of 3 to 6 independent measurements, each recorded to the nearest 0.1 cm. Height will be measured (using a stadiometer or length board) in all subjects during screening and at Day 1, Week 28, Week 52, Month 18 and every 6 months thereafter, and at early termination. Subjects who have grown less than 2.5 cm within the past year, have complete fusion of epiphyses on the hand/wrist radiograph, or are more than 2 years past menarche (females) are not required to have height measurement at Week 16 or Week 40. Height will be expressed in cm and in standard deviation scores (SDS) according to the Center for Disease Control (CDC) growth charts.

Weight will be measured using a digital scale as the average of 3 measurements and recorded to the nearest 0.1 kg with subjects not wearing shoes or outerwear (eg, jackets or coats). Weight will be expressed in kg and in SDS according to CDC growth charts.

Body mass index will be calculated as weight divided by height squared (kg/m^2) and expressed in SDS according to CDC growth charts.

BSA based on weight and height will be calculated using the DuBois Method.

9.3.4. Bone Age

Bone age will be assessed via x-ray (single posterior-anterior radiograph) of the left hand and wrist using the Greulich and Pyle method as specified in Table 7 and Table 8 as long as the most recent prior bone age was less than 14 years for females and less than 16 years for males. If there is a known history of trauma or surgery involving the left hand or wrist, the right hand and wrist can be used for bone age assessment. If bone age was assessed within 30 days of Day 1 and the film can be provided, this can be used for the Day 1 bone age. Otherwise, all x-rays will be acquired by the site and sent to a central imaging facility for evaluation. A study procedure manual will be provided by the central imaging facility that will include all x-ray related acquisition and submission details.

Subjects will be asked to provide films of a historical bone age, ie, the most recent bone age (only if a prior bone age was performed) that was obtained at least 6 months prior to the Day 1 bone age assessment, which will be sent for central reading. The Day 1 x-ray to assess bone age may be performed up to 7 days prior to the study visit. The time window for a bone age x-ray that needs to be repeated due to an inadequate initial scan is within 2 weeks of the actual study visit (including Day 1 visit). Bone age assessment is not required at the early termination visit if the subject had a bone age assessment within 3 months prior.

9.3.5. Fasting Lipids and Homeostatic Model Assessment of Insulin Resistance

Fasting blood tests will be obtained for the following assessments as specified in Table 7 and Table 8:

- 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)

9.3.6. Menstrual Cycle Questionnaire

The Menstrual Cycle Questionnaire will be used to assess regularity of menstrual cycles in females who have undergone menarche and are not on hormonal or intrauterine device 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 the screening visit.

Instructions for completing the Menstrual Cycle Questionnaire will be reviewed at the screening visit. Subject documentation of menstrual cycle information collected in the eDiary will be reviewed by the site as specified in Table 7 and Table 8.

9.3.7. Hirsutism and Acne Scales

Visual analog scales will be used to assess the subject's perception of severity of hirsutism (female subjects only) and acne. 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 as specified in Table 7 and Table 8.

9.3.8. Testicular Ultrasound

A testicular ultrasound will be performed at Day 1 in all male subjects to screen for adrenal rest tumors. Testicular ultrasound will be performed at Week 28, Week 52, and early termination if the Day 1 ultrasound demonstrates the presence of TARTs, as specified in Table 7 and Table 8. All male subjects continuing in the OLE will have a testicular ultrasound at Week 52 (Table 8), including subjects who were not required to have a Week 52 ultrasound as part of the core study (Table 7). An ultrasound will be performed at Month 24 and every 12 months thereafter only if the Week 52 ultrasound demonstrates the presence of TARTs. Testicular ultrasound may also be performed at additional time points if the investigator feels it is clinically indicated. Prior to Week 52, testicular ultrasound is not required at the early termination visit if the subject had a testicular ultrasound within 3 months prior.

The ultrasound will be acquired by the site and sent to a central imaging facility for evaluation. A study procedure manual will be provided by the central imaging facility that will include all ultrasound related acquisition and submission details. The results of any local reading will not need to be recorded by the site.

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. The Day 1 testicular ultrasound may be performed up to 7 days prior to the study visit. 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 study visit (including Day 1 visit).

9.4. Patient and Caregiver Reported Outcomes

9.4.1. EQ-5D

The EQ-5D-Y will be administered to subjects 8 to 15 years of age. This instrument has children self-report on 5 dimensions of health: Mobility, Looking After Myself, Usual Activities, Pain/Discomfort, and being Worried, Sad, or Unhappy. Each dimension has 3 levels of severity: "no problems", "some problems", or "a lot of problems" (Scott et al., 2017). The subject indicates his/her health state by checking the box next to the most appropriate statement. Subjects also rate their overall health on a 0 to 100 hash-marked, vertical visual analogue scale, where 100 is labeled "The best health you can imagine" and 0 is labeled "The worst health you can imagine." This instrument has been validated in international population samples of children and adolescents (Ravens-Sieberer et al., 2010).

The EQ-5D-5L will be administered to subjects ≥16 years of age. This instrument 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, where 100 is labeled "The best health you can imagine" and 0 is labeled "The worst health you can imagine."

The version of EQ-5D used in the OLE should be based on the subject's age at Month 12/Week 52.

9.4.2. Pediatric Quality of Life Instrument

The 23-item Pediatric Quality of Life Instrument (PedsQL™) Generic Core Scales encompass: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items) (Varni et al., 2001). The PedsQL has been shown to be a valid instrument in pediatric subjects (Varni et al., 2006). The instructions ask how much of a problem each item has been during the past one month. A 5-point Likert response scale is used (0=never a problem; 1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem). To further increase the ease of use for the young child self-report (ages 5 to 7), the response scale is reworded and simplified to a 3-point scale (0=not at all a problem; 2=sometimes a problem; 4=a lot of a problem), with each response choice anchored to a happy-to-sad faces scale. Items are reverse-scored and linearly transformed to a 0 to 100 scale, so that higher scores indicate better health-related quality of life.

The Toddler Version of the PedsQL will be used for subjects age 2 to 4 years, the Young Child Version will be used for subjects age 5 to 7 years, the Child Version for subjects age 8 to 12 years, and the Adolescent Version will be used for age 13 to 17 years. Children age 2 to 7 years will have the instrument read out loud to them; children age 8 to 17 years will read the instrument on their own.

The PedsQL will be administered as specified in Table 7. The PedsQL will not be assessed in the OLE.

9.4.3. Pediatric Quality of Life Family Impact Module

The PedsQL Family Impact Module is a 36-item instrument that include 6 scales measuring parent/caregiver self-reported functioning: 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items), 5) communication (3 items), 6), Worry (5 items), and 2 scales measuring parent-reported family functioning; 7) daily Activities (3 items) and 8) Family Relationships (5 items) (Varni et al., 2004). The PedsQL Family Impact Module was developed as a parent-report instrument. A 5-point response scale is used (0=never a problem; 4=always a problem). Items are reverse-scored and linearly transformed so that higher scores indicate better functioning. The reliability and validity of this instrument was demonstrated in families with children with complex chronic health conditions.

The PedsQL Family Impact Module will be administered as specified in Table 7 and will not be assessed in the OLE.

9.5. Pharmacokinetics

For all subjects, a blood sample for determination of plasma concentration of crinecerfont and metabolites will be collected approximately 15 minutes prior to the morning study drug dose at Weeks 4, 16, 28, 40, 52; it will also be collected at early termination, if early termination occurs prior to Week 52. At Week 4: for subjects who are ≥6 years of age with a body weight ≥30 kg, blood samples for PK will also be collected approximately 2, 3, 4, and 6 hours after dosing.

Subjects who have their evening dose doubled for inadequate efficacy during the OLE will have a study visit approximately 1 month after the dose increase, at which a single PK sample should be collected approximately 15 minutes prior to morning study drug dose; these same subjects will also have a single PK sample collected at the first 6-month visit following doubling of the evening dose. For example, a subject whose evening dose is doubled at Month 24 will have an extra visit with PK draw at Month 25 and will also have PK drawn at Month 30. Further PK samples will not be required during the OLE after the PK samples obtained approximately 1 month and 6 months following a dose increase for inadequate efficacy.

For each sample, approximately 2 mL of blood will be collected in tubes containing dipotassium ethylenediaminetetraacetic acid. The exact time of sampling in hours and minutes will be recorded for all PK plasma samples. A PK sample should be collected from subjects who terminate 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. Other Assessments

9.6.1. Palatability/Ease of Administration Assessment

Palatability of the study drug will be assessed by asking subjects ≥6 years of age to rate the taste and smell of the study drug, as well as how easy the study drug was to take, on a 5-point hedonic scale, with 5 being a favorable response and 1 being an unfavorable response. Each response is anchored to a face on a happy-to-sad scale. Subjects who found the taste to be “1 - Very Bad” or “2 – Bad” will be asked to identify what quality(ies) about the taste they didn't like. Palatability assessment at the early termination visit is not required if the subject has discontinued study drug.

For subjects 2 to 5 years of age, caregivers will be asked to rate the ease of administration of the study drug both on that day and overall on a 5-point hedonic scale with 5 indicating relative ease and 1 indicating relative difficulty. This assessment is adapted from the Caregiver-administered Children’s Acceptance Tool, which has been shown to be a reliable instrument in assessing pediatric acceptance of medicines (Blume et al., 2018).

The palatability/ease of administration assessment should be administered within approximately 15 minutes after study drug dosing as specified in Table 7.

9.6.2. Genotyping

At Week 4, a blood sample will be collected for CYP21A2 genotyping (only for subjects who have not previously had genotyping or are not able to provide records of prior genotyping). Genotyping blood samples will be shipped to a central laboratory for analysis.

9.7. Safety Assessments

Concomitant medication use and AEs will be monitored throughout the study as described in Section 9.10 and Section 11, respectively. Additional safety assessments are described in the following sections.

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.

9.7.1. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will periodically review ongoing unblinded clinical safety data to ensure the safety and well-being of the study subjects and also to confirm observed exposures are consistent with expected target exposures. The DMC consists of 5 members, including 4 physicians and 1 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 a recommendation for early termination of the study, changes to the protocol and informed consent based on unexpected adverse findings, or changes in the dose levels. The DMC will convene its first data review meeting after approximately 8 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 will be included in the DMC charter.

9.7.2. Events Requiring Glucocorticoid Stress Dosing

Subjects (and caregivers) should be educated on situations (such as illness or other events associated with significant physical stress) that require increased glucocorticoid dosing. Subjects may follow guidance provided by the investigator, their treating physician, or based on guidelines provided in Appendix A. Use of glucocorticoid stress dosing will be captured by subjects (or caregivers as appropriate) and documented in the eCRF.

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 children and adolescents based on stable isotope methodology (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 will evaluate subjects for any symptoms suggestive of glucocorticoid insufficiency using a standardized checklist.

Events that require glucocorticoid stress dosing, including those that require increased oral dosing, parenteral administration, emergency department evaluation, and/or hospital admission will be reviewed periodically (including by the DMC).

9.7.3. Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature (oral, rectal, ear, or forehead), 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, age-appropriate, calibrated automatic blood pressure cuff (with the exception of at-home visits) after the subject has been sitting quietly for at least 5 minutes.

Vital sign measurements will be obtained as specified in Table 7 and Table 8.

9.7.4. Medical History

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

9.7.5. 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, neurological, and genitourinary system.

9.7.5.1. Tanner Staging

Tanner staging (1 to 5) will include assessment of pubic hair (males and females), breast development (females), and genital development (males). Due to the subjectivity of Tanner genital staging for males, testicular volume will be assessed using a Prader orchidometer to assign a Tanner stage equivalent as follows: Tanner stage 1: <4 mL; Tanner stage 2: ≥4 mL and <8 mL; Tanner stage 3: ≥8 and <12 mL; Tanner stage 4: ≥12 and ≤15 mL; and Tanner stage 5: >15 mL (Nokoff et al., 2019). If genital staging by testicular volume (assessed with Prader orchidometer) differs from genital staging based on clinical appearance of the scrotum, testes, and penis, the Tanner genital stage for males should be based on testicular volume.

Tanner stage should be assessed in all subjects at screening and Day 1 (baseline). Historical assessment of Tanner staging is acceptable if Tanner stage 5 has been previously documented. Tanner stage will not be required to be assessed at Day 1 if the investigator determines that the Tanner stage is unlikely to have changed since screening; in this case, the screening Tanner stage will be considered the baseline. Subjects who are Tanner stage 5 do not need further assessment of Tanner stage at subsequent visits. Tanner stage is not required at Week 16 and Week 40 if baseline Tanner stage is 4.

Physical examinations and Tanner staging will be performed as specified in Table 7 and Table 8.

9.7.6. Electrocardiogram

A standard 6- or 12-lead ECG)(based on chest size) 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.

ECGs will be performed as specified in Table 7 and Table 8.

9.7.7. Clinical Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory. The central laboratory will provide instructions in a laboratory manual and supplies to the study sites.

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.

TSH and T4 levels: TSH and free T4 levels will be measured at screening (TSH only) and at scheduled time points during the study.

Cortisol: A blood sample to measure cortisol levels will be performed as specified in Table 7 and Table 8. If there is insufficient volume available in the blood sample collected, cortisol measurement may not be performed, and this is not considered a protocol deviation.

Urinalysis: casts, crystals, specific gravity, nitrite, ketones, protein, urobilinogen, glucose, bilirubin, 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.

Pregnancy Test: Pregnancy tests will be performed throughout the study for subjects of childbearing potential. A serum beta-human chorionic gonadotropin 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 as specified in Table 7 and Table 8.

9.7.8. Columbia-Suicide Severity Rating Scale

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu) and will be used only for subjects ≥6 years of age. There are versions of the questionnaire designed for use at screening (baseline/screening version) and at baseline and 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 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 lifetime history of suicidal behavior based on the C-SSRS should be excluded from participation in the study (see exclusion criterion #15).

The C-SSRS will be administered and scored by the investigator or qualified study center personnel as specified in Table 7 and Table 8.

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

9.7.9. Brief Psychiatric Rating Scale for Children

The Brief Psychiatric Rating Scale for Children (BPRS-c) is a clinician-rated tool designed to assess the severity of psychopathology in subjects with schizophrenia and other psychotic disorders (Mullins et al., 1986). The BPRS-c is a 21-item, clinician-based rating scale designed for use in evaluating psychiatric problems of children and adolescents. The severity of each item of the BPRS-c is rated on a scale of 0 (not present) to 6 (extremely severe) (total score range: 0 to 126). Higher scores represent greater symptom severity. The BPRS-c will be administered only to subjects ≥3 years of age. In the OLE, the BPRS-c will continue to be administered to subjects who are ≥18 years of age.

The investigator or other qualified site personnel will administer and score the BPRS-c as specified in Table 7 and Table 8.

9.7.10. Estimated Total Blood Sample Volume Required by Study

The approximate total blood volumes drawn from subjects on Day 1, at Week 4, and over the course of the study through Week 52/Week 56 are provided by age and weight group in Table 13 and for the OLE in Table 14. The volumes on Day 1 and Week 4 are described separately as these study visits may include serial sampling (depending on age/weight group) and represent the largest blood volumes drawn on a single day during the study.

Table 13: Approximate Total Blood Volumes Drawn from Subjects on Day 1, Week 4, and Over the Course of the Study up to Week 56

Age and Weight	Notes	Approximate Total Blood Volume Drawn		
		Day 1	Week 4	All Visits up to Week 56
<6 years or <20 kg	No serial sampling	24 mL	11 mL	202 mL
≥6 years and ≥20 kg to <30 kg	Serial sampling for 17-OHP and A4	44 mL	31 mL	254 mL
≥6 years and ≥30 kg	Serial sampling for 17-OHP, A4, ACTH, and (Week 4) PK	54 mL	49 mL	282 mL

17-OHP=17-hydroxyprogesterone; A4=androstenedione; ACTH= adrenocorticotropic hormone; PK=pharmacokinetics.

The volume of blood that will be collected at any visit for this study is below 3% of total blood volume, which has been demonstrated to be safe for blood draws in clinical trials of children as young as 6 months and up to 12 years old (Peplow et al., 2019). In this analysis of 3 clinical trials of 141 children (with treatment and monitoring over 12 to 18 months), blood draws of up to 3% of total blood volume at a single draw, or 2.4 mL/kg (assuming total blood volume =80 mL/kg), were not associated with symptoms or signs of anemia or hypovolemia during the trial.

Table 14: Approximate Total Blood Volumes Drawn from Subjects During the Open-Label Extension

Age and Weight	Approximate Total Blood Volume Drawn					
	Month 18 and Every 12 Months Thereafter	Month 24 and Every 12 Months Thereafter	One Month After Doubling of Evening Dose[a]	OLE ET	Final Study Visit (Last Dose of Study Drug + 4 weeks)	For Each Year in the OLE
<6 years or <20 kg	20 mL	24 mL	18 mL	24 mL	14 mL	44 mL (64 mL[a])
≥6 years and ≥20 kg	26 mL	30 mL	24 mL	30 mL	20 mL	56 mL (82 mL[a])

ET=early termination; OLE=open-label extension.
[a] Values in parentheses refer to subjects whose evening crinecerfont dose is doubled in the setting of inadequate efficacy, because they will have blood tests approximately 1 month later.

9.8. Specific Study Period Information

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

9.8.1.1. Screening Visit

All parents or legal guardians will provide informed consent with signed and witnessed pediatric assent for subjects determined by the investigator to be capable of providing assent according to national laws and regulations before the performance of any study-related procedures. Subjects will undergo screening for up to 4 weeks (Week -4 to Day -1) to determine eligibility. The screening period can be extended by up to 4 weeks after discussion with and approval of the Medical Monitor to allow for delayed screening laboratory results that are needed to determine eligibility or to accommodate other extenuating logistical issues, such as scheduling. After informed consent and assent have been obtained, subjects will be asked to take their evening glucocorticoid dose (the night before the visit) prior to 2100 hours and hold their morning dose of glucocorticoid and fludrocortisone (if applicable) until after blood sample collection, with dosing to occur between approximately 0800 and 0830 hours. During the screening period, blood sample collection may be performed at home.

The following study procedures and assessments will be performed:

- Obtain informed consent/pediatric assent.
- Assess inclusion/exclusion criteria.
- Review and record medical history.
- Perform a physical examination, including Tanner stage. Historical assessment of Tanner staging is acceptable if Tanner stage 5 has been previously documented.
- Perform vital signs, including height and weight.
- Collect blood samples for TSH; serum pregnancy test only for subjects of childbearing potential; chemistry, hematology, and coagulation labs; 17-OHP, A4,

cortisol, LH, FSH, testosterone, and PRA (prior to morning glucocorticoid and [if applicable] fludrocortisone dose).

- Collect urine for urine drug screen (only for subjects ≥12 years of age) and urinalysis.
- Administer the BPRS-c (only for subjects ≥3 years of age) and C-SSRS (Screening/baseline version; only for subjects ≥6 years of age).
- Perform 6- or 12-lead ECG.
- Provide eDiary to record daily glucocorticoid doses.
- Review instructions for the Menstrual Cycle Questionnaire (only in females who have undergone menarche and 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.

9.8.2. Randomized, Double-Blind, Placebo-Controlled Treatment Period (Day 1 up to Week 28)

9.8.2.1. Baseline (Day 1)

Baseline/Day 1 is defined as the first day of study drug dosing and should be the same as the day of randomization in the IRT.

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid and fludrocortisone (if applicable) on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- 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 Tanner stage. Tanner stage will not be required to be assessed at Day 1 if the investigator determines that the Tanner stage is unlikely to have changed since screening; in this case, the screening Tanner stage will be considered the baseline.
- Perform vital signs, height, and weight.
- Collect blood samples for chemistry, TSH, free T4, hematology, and coagulation labs; fasting lipids and HOMA-IR; cortisol, LH, FSH, testosterone, PRA.

- Collect blood samples for 17-OHP, A4, and ACTH.
  - For subjects who are ≥6 years of age with a body weight ≥20 kg: approximately 15 minutes before and just prior to dosing with the morning glucocorticoid and at 2, 3, 4, and 6 hours after dosing. Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose blood sample collection. For subjects with body weight ≥20 to <30 kg, only a single sample for ACTH will be collected, which will be the sample just prior to the morning glucocorticoid dose.
  - For subjects who are <6 years of age or with a body weight <20 kg: blood sample collected prior to dosing with the morning glucocorticoid.
- Collect urine sample for urinalysis and (only for subjects of childbearing potential) urine pregnancy test.
- Collect salivary samples for hormone assessment at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid dosing and 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of glucocorticoid; if subject is not on an evening glucocorticoid dose, then prior to bedtime.
- Perform x-ray to assess bone age (only in females with the most recent bone age <14 years and in males with the most recent bone age <16 years; see Section 9.3.4).
- Perform testicular ultrasound (males only).
- Administer the EQ-5D (EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for age 16 to 17 years); the PedsQL (PedsQL Toddler Version for age 2 to 4 years, Young Child Version for age 5 to 7 years, Child Version for age 8 to 12 years, Adolescent Version for age 13 to 17 years); and the PedsQL Family Impact.
- Administer the BPRS-c (only for subjects ≥3 years); and the C-SSRS (Since Last Visit version; only for subjects ≥6 years).
- Administer the Hirsutism (female subjects only) and Acne Scales.
- Review the Menstrual Cycle Questionnaire (only females who have undergone menarche and are not on hormonal or intrauterine device contraceptives).
- Perform 6- or 12-lead ECG.
- 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 (each dose separated by approximately 12 hours).
- Record concomitant medications.
- AE monitoring.

9.8.2.2. Week 4 (±5 days)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Perform vital signs and weight.
- Collect urine sample for urine pregnancy test (only for female subjects of childbearing potential).
- Collect PK blood sample(s).
  - For subjects who are ≥6 years of age with a body weight ≥30 kg: approximately 15 minutes before (or just prior to) dosing with the morning glucocorticoid and study drug and at 2, 3, 4, and 6 hours after dosing.
  - For subjects <6 years of age or <30 kg: blood sample collection prior to dosing with the morning glucocorticoid and study drug.
- Collect blood for 17-OHP, A4, and ACTH assessments.
  - For subjects who are ≥6 years of age with a body weight ≥20 kg: approximately 15 minutes before and just prior to dosing with the morning glucocorticoid and study drug and at 2, 3, 4, and 6 hours after dosing. For subjects with body weight ≥20 to <30 kg, only a single sample for ACTH will be collected, which will be the sample just prior to the morning glucocorticoid dose.
  - For subjects who are <6 years of age or with a body weight <20 kg: blood sample collection prior to dosing with the morning glucocorticoid and study drug.
- Collect blood sample for CYP21A2 genotyping.
- Collect salivary samples for hormone assessment at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid and study drug dosing and 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of glucocorticoid; if subject is not on an evening glucocorticoid dose, then prior to bedtime.
- Administer the C-SSRS (Since Last Visit version; only for subjects ≥6 years).
- Review the Menstrual Cycle Questionnaire data (only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives).
- Administer the palatability/ease of administration assessment (palatability will be assessed by subjects ≥6 years of age, and ease of administration will be assessed by caregivers for subjects <6 years of age) within approximately 15 minutes after study drug dosing.
- Perform 6- or 12-lead ECG.
- Dispense study drug.
- Study drug accountability.

- Record concomitant medications.
- AE monitoring.

The investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any follow-up needed.

9.8.2.3. Week 8 (±7 days; at home or the study site)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Collect blood samples for clinical chemistry, 17-OHP, A4, and cortisol.
- Collect salivary sample for hormone assessment at approximately the same time as the blood sample.
- AE monitoring.

The investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any follow-up needed.

9.8.2.4. Week 12 (±7 days; at home or the study site; only if a preceding glucocorticoid dose adjustment occurred)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Collect blood samples for clinical chemistry, 17-OHP, A4, and cortisol.
- Collect salivary sample for hormone assessment at approximately the same time as the blood sample.
- AE monitoring.

The investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any follow-up needed.

9.8.2.5. Week 16 (±7 days; at home [unless height measurement needed] or the study site)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Perform vital signs, height (subjects who have grown less than 2.5 cm within the past year, have evidence of fused epiphyses on bone age x-rays, or are more than 2 years past menarche [females] are not required to have height measurement), and weight.
- Assess Tanner stage (only if Tanner stage <4 on Day 1).
- Collect blood samples for chemistry, hematology, and coagulation labs; PK (prior to study drug); 17-OHP, A4, cortisol, ACTH, LH, FSH, testosterone, and PRA.
- Collect urine sample for urine pregnancy test (only for subjects of childbearing potential).
- Collect salivary sample for hormone assessment at approximately the same time as the blood sample.
- Administer the C-SSRS (Since Last Visit version; only for subjects ≥6 years).
- Review the Menstrual Cycle Questionnaire data (only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives).
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

The investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any follow-up needed.

9.8.2.6. Week 20 (±7 days; at home or the study site; only if a preceding glucocorticoid dose adjustment occurred)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and

study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Collect blood sample for 17-OHP and A4.
- Collect salivary sample for hormone assessment at approximately the same time as the blood sample.
- AE monitoring.

9.8.2.7. Week 28 (±7 days; all Week 28 assessments should be completed before a subject begins open-label treatment)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Perform a physical examination.
- Perform vital signs, height, and weight.
- Assess Tanner stage (only if Tanner stage <5 on Day 1).
- Collect blood samples for chemistry, TSH, free T4, hematology, and coagulation labs; PK (prior to morning study drug); fasting lipids and HOMA-IR; 17-OHP, A4, cortisol, ACTH, LH, FSH, testosterone, and PRA prior to dosing.
- For subjects ≥6 years of age with body weight ≥20 kg, also collect blood samples for 17-OHP, A4, and ACTH approximately 3 hours after glucocorticoid and study drug administration.
- Collect urine sample for urinalysis and (only for female subjects of childbearing potential) urine pregnancy test.
- Collect salivary samples for hormone assessment at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid dosing and 3 and 6 hours after dosing (any midday glucocorticoid dose that the subject is receiving should be taken after the salivary sample collection 6 hours after dosing), and within 30 minutes prior to the evening dose of glucocorticoid; if subject is not on an evening glucocorticoid dose, then prior to bedtime.

- Perform x-ray to assess bone age (only in females with the most recent bone age <14 years and in males with the most recent bone age <16 years; see Section 9.3.4).
- Perform testicular ultrasound (males only; only if evidence of TART on Day 1 ultrasound).
- Administer the EQ-5D (EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for age 16 to 17 years); the PedsQL (PedsQL Toddler Version for age 2 to 4 years, Young Child Version for age 5 to 7 years, Child Version for age 8 to 12 years, Adolescent Version for age 13 to 17 years); and the PedsQL Family.
- Administer the BPRS-c (only for subjects ≥3 years); and the C-SSRS (Since Last Visit version; only for subjects ≥6 years).
- Administer the Hirsutism (female subjects only) and Acne Scales.
- Review the Menstrual Cycle Questionnaire data (only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives).
- Administer the palatability/ease of administration assessment (palatability will be assessed by subjects ≥6 years of age, and ease of administration will be assessed by caregivers for subjects <6 years of age) within approximately 15 minutes after study drug dosing.
- Perform 6- or 12-lead ECG.
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

9.8.3. Open-Label Treatment Period (Week 32 to Week 52/Early Termination)

9.8.3.1. Week 32 (±7 days; at home or the study site)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Collect blood samples for clinical chemistry, 17-OHP, A4, and cortisol.
- Collect salivary sample for hormone assessment at approximately the same time as the blood sample.
- AE monitoring.

The investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any follow-up needed.

9.8.3.2. Week 36 (±7 days; at home or the study site; only if a preceding glucocorticoid dose adjustment occurred)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Collect blood samples for clinical chemistry, 17-OHP, A4, and cortisol.
- Collect salivary sample for hormone assessment at approximately the same time as the blood sample.
- AE monitoring.

The investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any follow-up needed.

9.8.3.3. Week 40 (±7 days; at home [unless height measurement is needed] or the study site)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Perform vital signs, height (subjects who have grown less than 2.5 cm within the past year, have evidence of fused epiphyses on bone age x-rays, or are more than 2 years past menarche [females] are not required to have height measurement), and weight.
- Assess Tanner stage (only if Tanner stage <4 on Day 1).
- Collect blood samples for chemistry, hematology, and coagulation labs; PK (prior to morning study drug); 17-OHP, A4, cortisol, ACTH, LH, FSH, testosterone, and PRA.

- Collect urine sample for urine pregnancy test (only for subjects of childbearing potential).
- Collect salivary sample for hormone assessment at approximately the same time as the blood sample.
- Administer the C-SSRS (Since Last Visit version; only for subjects ≥6 years).
- Review the Menstrual Cycle Questionnaire data (only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives).
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

The investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any follow-up needed.

9.8.3.4. Week 44 (±7 days; at home or the study site; only if a preceding glucocorticoid dose adjustment occurred)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Collect blood sample for 17-OHP and A4.
- Collect salivary sample for hormone assessment at approximately the same time as the blood sample.
- AE monitoring.

9.8.3.5. Week 52 (±7 days)/Early Termination for Subjects Who Discontinue Prior to Week 52

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom

the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Perform a physical examination.
- Perform vital signs, height, and weight.
- Assess Tanner stage (only if Tanner stage <5 on Day 1).
- Collect blood samples for chemistry, TSH, free T4, hematology, and coagulation labs; PK (prior to morning study drug); fasting lipids and HOMA-IR; 17-OHP, A4, cortisol, ACTH, LH, FSH, testosterone, and PRA prior to dosing.
- For subjects ≥6 years of age with body weight ≥20 kg, also collect blood samples for 17-OHP, A4, and ACTH approximately 3 hours after glucocorticoid and study drug administration.
- Collect urine sample for urinalysis and (only for subjects of childbearing potential) urine pregnancy test.
- Collect salivary samples for hormone assessment at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid dosing and 3 and 6 hours after dosing (any midday glucocorticoid dose that the subject is receiving should be taken after the salivary sample collection 6 hours after dosing), and within 30 minutes prior to the evening dose of glucocorticoid; if subject is not on an evening glucocorticoid dose, then prior to bedtime.
- Perform x-ray to assess bone age (only in females with the most recent bone age <14 years and in males with the most recent bone age <16 years; see Section 9.3.4).
- Perform testicular ultrasound (males only; only if evidence of TARTs on Day 1 ultrasound).
- Administer the EQ-5D (EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for age 16 to 17 years); the PedsQL (PedsQL Toddler Version for age 2 to 4 years, Young Child Version for age 5 to 7 years, Child Version for age 8 to 12 years, Adolescent Version for age 13 to 17 years); and the PedsQL Family.
- Administer the BPRS-c (only for subjects ≥3 years); and the C-SSRS (Since Last Visit version; only for subjects ≥6 years).
- Administer the Hirsutism (female subjects only) and Acne Scales.
- Review the Menstrual Cycle Questionnaire data (only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives).
- Administer the palatability/ease of administration assessment (palatability will be assessed by subjects ≥6 years of age, and ease of administration will be assessed by caregivers for subjects <6 years of age) within approximately 15 minutes after study drug dosing.
- Perform 6- or 12-lead ECG.
- Study drug accountability.

- Record concomitant medications.
- AE monitoring.

9.8.4. Open-Label Extension (Month 12 [Week 52] Onwards)

9.8.4.1. Month 12 (Week 52 [±7 days])

At the Month 12 visit, if subject will be continuing into the OLE, perform the study procedures listed in Section 9.8.3.5 and the following:

- Review applicable portions of the ICF and assent form (if applicable) and confirm participation in the optional OLE.
- Dispense study drug.
- Perform testicular ultrasound (all male subjects, even if not required as part of Week 52 assessments in Section 9.8.3.5).

If a glucocorticoid dose reduction is performed, investigator should contact subject/guardian within 2 weeks to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.8.4.2. Month 13 or Every 6 Months Thereafter (Months 19, 25, 31, etc ±7 days relative to the preceding visit) (only for subjects who had their evening dose doubled at the preceding study visit)

Subjects who had their evening crinecerfont dose doubled in the setting of inadequate efficacy, as determined at any of the study visits scheduled every 6 months during the OLE, will have a study visit approximately 1 month later. Dose can be increased for inadequate efficacy once at the specified weight-based dose (eg, 50 mg BID can be increased to 50 mg qam and 100 mg qpm) but not further unless the subject crosses into the next weight category.

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours (±1 hour) with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Perform physical examination.
- Collect vital signs and weight.
- Collect blood samples for PK, chemistry, 17-OHP, A4, cortisol, ACTH, LH, FSH, testosterone, and PRA prior to dosing.
- Perform 6- or 12-lead ECG.
- Record concomitant medications.

- AE monitoring.

The investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any follow-up needed (Section 9.3.2.3).

9.8.4.3. Month 18 and Every 12 Months Thereafter (Month 30, 42, 54, etc ±14 days)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Assess Tanner stage (only if most recent Tanner stage <5).
- Perform vital signs, height, and weight.
- Collect blood sample for PK (only for subjects who had their evening dose of crinecerfont doubled at the previous 6-month visit; further PK samples will not be required during the OLE after the PK samples obtained approximately 1 month and 6 months following a dose increase for inadequate efficacy).
- Collect blood samples for chemistry, hematology, and coagulation labs; fasting lipids and HOMA-IR; 17-OHP, A4, cortisol, ACTH, LH, FSH, testosterone, and PRA prior to dosing.
- Collect blood sample for PK (only for subjects who had their evening dose of crinecerfont doubled at the previous 6-month visit; further PK samples will not be required during the OLE after the PK samples obtained approximately 1 month and 6 months following a dose increase for inadequate efficacy).
- Perform x-ray to assess bone age (only in females with the most recent bone age <14 years and in males with the most recent bone age <16 years; see Section 9.3.4).
- Administer the C-SSRS (Since Last Visit version; only for subjects ≥6 years of age).
- Administer the Hirsutism (female subjects only) and Acne Scales.
- Review the Menstrual Cycle Questionnaire data (only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives).
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

The investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any follow-up needed (Section 9.3.2.3).

If a glucocorticoid dose reduction occurs, the investigator should contact subject/guardian within 2 weeks to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.8.4.4. Month 24 and Every 12 Months Thereafter (Month 36, 48, 60, etc. ±14 days)

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid, fludrocortisone (if applicable), and study drug on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

Subjects should be fasting, with no food from midnight the previous night until after the predose blood sample collection, after which they can have breakfast; subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) if needed but should wait to have breakfast until after blood sample collection.

The following study procedures and assessments will be performed:

- Perform a physical examination.
- Assess Tanner stage (only if most recent Tanner stage <5).
- Perform vital signs, height, and weight.
- Collect blood sample for PK (only for subjects who had their evening dose of crinecerfont doubled at the previous 6-month visit; further PK samples will not be required during the OLE after the PK samples obtained approximately 1 month and 6 months following a dose increase for inadequate efficacy).
- Collect blood samples for chemistry, hematology, and coagulation labs; TSH and free T4; fasting lipids and HOMA-IR; 17-OHP, A4, cortisol, ACTH, LH, FSH, testosterone, and PRA prior to dosing.
- For subjects ≥6 years of age with body weight ≥20 kg, also collect blood samples for 17-OHP, A4, and ACTH approximately 3 hours after glucocorticoid and study drug administration.
- Collect salivary samples over the course of the day: at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid and study drug dosing and 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of glucocorticoid (if subject is not taking evening glucocorticoid dose, then prior to bedtime). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose salivary sample is collected.
- Collect urine sample for urinalysis and (only for subjects of childbearing potential) urine pregnancy test.
- Perform x-ray to assess bone age (only in females with the most recent bone age <14 years and in males with the most recent bone age <16 years; see Section 9.3.4).

- Perform testicular ultrasound (males only; only if evidence of TART on Week 52/Month 12 ultrasound).
- Administer the EQ-5D (EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for ≥16 years of age; based on age at Month 12/Week 52).
- Administer the BPRS-c (only for subjects ≥3 years of age) and the C-SSRS (Since Last Visit version; only for subjects ≥6 years of age).
- Administer the Hirsutism (female subjects only) and Acne Scales.
- Review the Menstrual Cycle Questionnaire data (only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives).
- Dispense study drug.
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

The investigator will contact the subject/guardian once laboratory results are available in order to instruct the subject/guardian on any glucocorticoid dose changes and arrange any follow-up needed (Section 9.3.2.3).

If a glucocorticoid dose reduction occurred, investigator should contact subject/guardian within 2 weeks to perform a safety follow-up and assess whether the subject is tolerating the glucocorticoid dose reduction.

9.8.4.5. Open-Label Extension Early Termination

The following study procedures and assessments will be performed:

- Perform a physical examination.
- Assess Tanner stage (only if most recent Tanner stage <5).
- Perform vital signs, height, and weight.
- Perform 6- or 12-lead ECG.
- Collect blood samples for chemistry, hematology, and coagulation labs; fasting lipids and HOMA-IR; 17-OHP, A4, cortisol, ACTH, LH, FSH, testosterone, and PRA.
- For subjects ≥6 years of age with body weight ≥20 kg, also collect blood samples for 17-OHP, A4, and ACTH approximately 3 hours after glucocorticoid and study drug administration.
- Collect salivary samples over the course of the day: at approximately 0600 hours, at approximately 0800 hours prior to morning glucocorticoid and study drug dosing and 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of glucocorticoid (if subject is not taking evening glucocorticoid dose, then prior to bedtime). Any midday glucocorticoid dose that the subject is receiving should be taken after the 6-hour postdose salivary sample is collected.

- Collect urine sample for urinalysis and (only for subjects of childbearing potential) urine pregnancy test.
- Perform x-ray to assess bone age (only in females with the most recent bone age <14 years and in males with the most recent bone age <16 years; see Section 9.3.4).
- Perform testicular ultrasound (all male subjects). Testicular ultrasound is not required at the early termination visit if the subject had a testicular ultrasound within 3 months prior.
- Administer the EQ-5D (EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for age ≥16 years; based on age at Week 52).
- Administer the BPRS-c (only for subjects ≥3 years of age); and the C-SSRS (Since Last Visit version; only for subjects ≥6 years of age).
- Administer the Hirsutism (female subjects only) and Acne Scales.
- Review the Menstrual Cycle Questionnaire data (only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives).
- Study drug accountability.
- Record concomitant medications.
- AE monitoring.

9.8.5. Follow-up Period: Final Study Visit (+14 days; 4 weeks after last dose of study drug)

This visit is not required if the last dose of study drug was at least 4 weeks prior to the early termination visit, or if the subject transitions during the OLE to commercially available crinecerfont or to another crinecerfont study.

Subjects should take their evening glucocorticoid dose prior to 2100 hours the night before the visit and should hold their morning dose of glucocorticoid and fludrocortisone (if applicable) on the day of the visit until after the predose blood sample collection, with dosing to occur between approximately 0800 and 0830 hours with breakfast.

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 vital signs and weight.
- Collect blood samples for chemistry, hematology, and coagulation labs; 17-OHP, A4, ACTH, and cortisol.
- Collect urine sample for urinalysis and (only for subjects of childbearing potential) urine pregnancy test.
- Review the Menstrual Cycle Questionnaire data (only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives).
- Administer the C-SSRS (Since Last Visit version; only for subjects ≥6 years of age).

- Perform 6- or 12-lead ECG (only for subjects who do not participate in the OLE).
- Record concomitant medications.
- AE monitoring.

9.9. Study Duration

The expected duration of study participation for each subject is approximately 60 weeks, plus a variable amount of time in the OLE (estimated average of approximately 24 months), including 4 weeks for screening, 28 weeks of blinded placebo-controlled treatment, and 24 weeks of open-label treatment, a variable amount of time in the OLE, and 4 weeks of follow-up.

9.10. Prohibitions and Restrictions

9.10.1. 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.

Corticosteroids

During the screening period, subjects should maintain a stable glucocorticoid and (if applicable) mineralocorticoid regimen unless the subject requires glucocorticoid stress dosing for illness or other significant physical stress. The importance of adherence to their glucocorticoid and mineralocorticoid regimen should be emphasized 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 the 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 a stable fludrocortisone dose to the extent possible during the study. Increases in PRA suggestive of insufficient mineralocorticoid replacement should be managed by first ensuring adequate salt intake before adjusting fludrocortisone dose.

Prohibited and Restricted 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.

- Exogenous testosterone treatment (eg, patients with XX chromosomes and male gender identity).

The following medications have restrictions or requirements regarding use prior to and/or during the study:

- Gonadotropin-releasing hormone agonist therapy for treatment of precocious puberty is allowed if the dose is stable for at least 3 months prior to screening OR if there is evidence of adequate pubertal suppression according to the investigator's judgment.
  - Therapy should not be commenced or discontinued during the randomized phase of the study.
  - Discontinuation or start of therapy is allowed based on the investigator's judgment during the open-label phase of the study.
  - Subjects who were previously treated with these medications should have discontinued at least 3 months prior to screening.
- Growth hormone therapy and aromatase inhibitors (eg, anastrozole, letrozole, testolactone) are allowed if the dose is stable for at least 1 month prior to screening.
  - Therapy should not be commenced or discontinued during the randomized phase of the study.
  - Discontinuation or start of therapy is allowed based on the investigator's judgment during the open-label phase of the trial.
  - Subjects who were previously treated with these medications should have discontinued at least 1 month prior to screening.
- Anti-androgens (eg, spironolactone, flutamide) are excluded but oral contraceptives with anti-androgenic progestins (eg, drospirenone, cyproterone acetate) are allowed if the subject has been on stable therapy for at least 3 months prior to screening.
  - Subjects who were previously treated with oral contraceptives should have discontinued at least 3 months prior to screening.

If any of the above medications have been administered during the year preceding screening or during the study, their use should be captured on the Prior and Concomitant Medications eCRF.

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 during 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 or intrauterine hormone-releasing system
- 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

9.10.2. Dietary and Other Restrictions

For all scheduled study visits at which a blood test is obtained (except the ones noted below), subjects should be fasting after midnight the night before until after the predose blood sample collection(s), and then take their morning glucocorticoid, fludrocortisone (if applicable), and (for all visits after Day 1) study drug dose with breakfast. Fasting is not required at the screening visit, the Week 56 visit for subjects who do not enter the OLE, or at the final study visit in the OLE. Subjects <6 years of age for whom the investigator deems that fasting until 0800 hours is not feasible can have a snack(s) but should wait to have breakfast until after the blood sample is collected. Subjects are encouraged to drink water to avoid hypovolemia.

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 is prohibited for at least 30 days after the last dose of study drug in the current study.

9.11. Discontinuation of Study Drug and Subject Withdrawal

Parent/legal guardian (or the subject, if the subject has reached the age of majority) can discontinue study drug or withdraw their consent for the subject to participate in the study at any time during the core study or during the OLE. 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 Week 52 should continue study participation to be followed for safety and efficacy outcomes up to the Week 52 visit; subjects who discontinue study drug dosing during the OLE will be withdrawn. Subjects who discontinue study drug prior to Week 52 are ineligible for the OLE.

9.11.1. 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 Week 52 will not be automatically withdrawn from the study and should continue participation in the study through Week 52. Data for any outcome measures, particularly the primary and secondary endpoints, as well as safety follow-up, are important to collect through the Week 52 visit. A PK sample should be collected within approximately 4 weeks of the last study drug dose, after which additional PK sampling would not be required. 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 9.10.1 is no longer prohibited after study drug discontinuation. Following discontinuation of study drug, the subject's glucocorticoid dose should be monitored and adjusted to achieve control of androgen levels as appropriate for that subject. Palatability of the study drug at the early termination visit is not required if the subject has discontinued study drug.

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.

9.11.2. Withdrawal from Study

If a subject prematurely withdraws from the study (either prior to Week 52 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 and, unless consent has been withdrawn, will be asked to come back approximately 4 weeks after their last dose of study drug for the final study visit (safety follow-up visit). If a subject's last dose of study treatment was >4 weeks before the early termination visit, no safety follow-up visit is needed. Subjects who complete the Week 52 visit but elect not to participate in the optional OLE will be considered to have completed the initial 52-week study; this will not be considered a premature withdrawal unless the subject does not return for a required Week 56/safety follow-up visit.

Reasons for withdrawal from study are:

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

9.11.3. 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 IECs/IRBs, 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(s) 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 or oral solution containing 50 mg of crinecerfont free base per 1 mL administered via a graduated oral dosing syringe.

For subjects randomized on Day 1 to receive crinecerfont, based on the Day 1 body weight, subjects 10 to <20 kg will receive crinecerfont 25 mg bid via oral solution, subjects 20 to <55 kg will receive crinecerfont 50 mg bid via oral solution, and subjects ≥55 kg will receive crinecerfont 100 mg bid via oral capsules through Week 28. Starting at Week 28 and continuing through Week 52, subjects will receive open-label crinecerfont according to the dosing guideline above based on their Week 28 body weight. Subjects should take the study drug with breakfast and evening meals.

At Month 12, subjects taking crinecerfont 50 mg bid or higher may elect to have their study drug dispensed as either oral solution or oral capsules. During the OLE, the crinecerfont dose should be based on the subject's weight at the study visit (25 mg bid if weight is 10 to <20 kg, 50 mg bid if weight is 20 to <55 kg, 100 mg bid if weight is ≥55 kg). Starting at Month 12, if the subject has inadequate efficacy (in the opinion of the investigator), the crinecerfont dose can be increased by doubling the evening dose.

10.2. Placebo

Placebo oral solution is identical in appearance and flavored identically to crinecerfont oral solution. Placebo capsules are identical in appearance to crinecerfont capsules. Placebo oral solution and capsules will be used to maintain the blind during the placebo-controlled treatment period.

10.3. Study Drug Supplies

Neurocrine Biosciences, Inc. (NBI) or its designee will provide the study center with sufficient study drug supplies for the completion of the study.

Crinecerfont capsules will be provided in blister cards through Week 52 and may be supplied in either blister cards or bottles during the OLE at the discretion of the Sponsor.

During the OLE, study drug will be dispensed every 3 months.

Crinecerfont oral solution will be provided in bottles with graduated oral dosing syringes and press-in bottle adapters to facilitate dispensing.

To ensure continued access to study treatment, if a subject is unable to go to the site when study treatment is to be dispensed, study treatment may be delivered from the site's pharmacy to the subject's residence by a distributor independent from the Sponsor. Study drug may be returned via the independent distributor. 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 the study drug (capsules or liquid) by mouth beginning with the evening meal on Day 1 (Note: Day 1 defined as the first day of study drug dosing and should be the same as the day of randomization in the IRT), 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. On days when blood samples are to be collected, the morning dose of study drug will be taken between approximately 0800 and 0830 hours with breakfast and after the pre-morning glucocorticoid dose blood sample collection.

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 9.10 for restrictions regarding study drug administration.

10.6. Study Drug Storage

Crinecerfont should be stored in a locked area accessible only to the pharmacist or designee until dispensing. Crinecerfont capsules should be stored refrigerated (2° to 8°C [36° to 46°F]) at all times. Unopened bottles of crinecerfont oral solution should be stored refrigerated (2° to 8°C [36° to 46°F]) until ready for use. After opening a bottle for dosing, store at room temperature (15° to 30°C [59° to 86°F]) for use up to 60 days.

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

10.7. Blinding

This study includes a 28-week double-blind, placebo-controlled treatment period, followed by a 24-week open-label treatment period during which all subjects will receive crinecerfont, and then by an OLE during which all subjects will receive crinecerfont.

The subject, investigator, and all study center personnel (with the exception of clinical trial material supply chain personnel who are not involved in decisions regarding subject's treatment) 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 28 visit, at which time a limited number of Sponsor personnel will be unblinded to conduct the Week 28 final analysis. Sponsor personnel with direct contact with the study site will remain blinded to individual subjects' randomized treatment assignment(s) until unblinding will no longer jeopardize the integrity of the study.

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 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 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. The investigator must document the date, time, and the reason the blind was broken.

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.

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/parent/legal guardian, noted from laboratory findings, or identified by other means, will be recorded from the time the parent/legal guardian 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 15, 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 15: 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 16. 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 United States [US] Code of Federal Regulations [CFR] 312.32 [a]).

Table 16: 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 subject 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.

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 pregnancies, contact DSPV:

DSPV facsimile: **+1 (888) 617-7551 or +1 (858) 617-7561**

DSPV email: **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. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the study treatment, and this new event is likely to affect the safety of subjects, the Sponsor and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard. The Sponsor will work with the investigator to ensure the Research Ethics Committee is notified within 3 days.

11.6. Pregnancy

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in females 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 (inclusion criterion #8 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 will be discontinued from study treatment, will be withdrawn from the study, and will be unblinded (if conception occurred during the double-blinded treatment period).

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 will 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 US CFR 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 (PI) 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 PI 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. A comprehensive and detailed statistical analysis plan (SAP) will be generated and finalized prior to any treatment unblinding. 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 change from baseline in serum A4 at Week 4, in all randomized subjects, regardless of adherence to study drug. Subjects who are missing serum A4 levels at all time points at the Week 4 visit 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 any subject in the placebo treatment group. For subjects in the placebo treatment group, missing data will be imputed using observed data from any subject 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 change from baseline in serum A4 at Week 4. In other words, H_0: $\mu_1=\mu_2$ where μ_1 is the mean change from baseline in serum A4 in the placebo group at Week 4 and μ_2 is the mean change from baseline in serum A4 in the crinecerfont treatment group at Week 4. The alternative hypothesis is that there is a difference between the crinecerfont and placebo treatment groups in the mean change from baseline in serum A4 at Week 4 (ie, H_1: $\mu_1 \neq \mu_2$).

13.4. Sample Size Determination

The sample size of 81 subjects (54 in the crinecerfont treatment group and 27 in the placebo group) is based on a power calculation for the primary endpoint (change from baseline in serum A4 at Week 4). In Study NBI-74788-CAH2001, the mean change from baseline to Day 14 in A4 was -286.2 ng/dL with a standard deviation of 345.02 (pooled across dosing cohorts). Based on a 2-sample t-test with an effect size of 0.83, a sample size of 81 subjects will have greater than 90% power to detect a treatment difference at a 0.05 level of significance. With an effect size as small as 0.70, a sample size of 81 subjects will have greater than 80% power to detect a treatment difference at the same level of significance.

13.5. Analysis Sets

The analysis sets to be used for the analyses described in this protocol are defined in Table 17. Additional analysis sets may be specified in the SAP.

Table 17: 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.
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 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.

In the event that the glucocorticoid dose is alternating, the average dose over 2 consecutive days will be used for glucocorticoid dosing endpoints.

13.6.1. Efficacy Analyses

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

13.6.1.1. Procedure to Control for Multiple Comparisons

A fixed-sequence testing procedure will be followed for the primary and key secondary efficacy endpoint analyses to control for the treatment group comparisons of multiple endpoints. The fixed-sequence testing procedure will consist of performing the hypothesis tests in the following prespecified order:

1. Primary endpoint: change from baseline in serum A4 at Week 4
2. Key secondary endpoint: change from baseline in serum 17-OHP at Week 4
3. Key secondary endpoint: percent change from baseline in daily glucocorticoid dose (in hydrocortisone dose equivalents adjusted for BSA) at Week 28, while Week 28 serum A4 is ≤120% of the baseline value or ≤ ULN, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5)

Each step in the sequential testing procedure will use a 2-sided 0.05 level of significance for the null hypothesis being tested. Testing of hypotheses at each step of the procedure commences only if all null hypotheses in prior steps were rejected.

All other p-values will not be adjusted for multiplicity and should be considered nominal p-values.

13.6.1.2. Primary Endpoint

The primary endpoint is the change from baseline in serum A4 at Week 4. Both baseline and Week 4 serum A4 values for subjects ≥6 years of age with a body weight ≥20 kg will be calculated as the average of all serum A4 values obtained from serial sampling on Day 1 and Week 4, respectively (subjects <6 years of age or <20 kg will have only a single serum A4 value for both baseline and Week 4). The primary analysis of the primary endpoint will be performed using an analysis of covariance (ANCOVA) model. The model will include treatment group, baseline serum A4, and stratification factors used in the randomization. Subjects who are missing serum A4 levels at all time points at the Week 4 visit 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 any subject in the placebo treatment group. For subjects in the placebo treatment group, missing data will be imputed using observed data from any subject in the placebo treatment group. 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 17-OHP at Week 4. Both baseline and Week 4 serum 17-OHP values for subjects ≥6 years of age with a body weight ≥20 kg will be calculated as the average of all serum 17-OHP values obtained from serial sampling on Day 1 and Week 4, respectively (subjects <6 years of age or <20 kg will have only a single serum 17-OHP value for both baseline and Week 4). The primary analysis of this endpoint will be performed using an ANCOVA model. The model will include treatment group, baseline serum 17-OHP, and stratification factors used in the randomization. Subjects who are missing serum 17-OHP levels at all time points at the Week 4 visit 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 any subject in the placebo treatment group. For subjects in the placebo treatment group, missing data will be imputed using observed data from any subject in the placebo treatment group.

The second key secondary endpoint is the percent change from baseline in glucocorticoid daily dose (in hydrocortisone dose equivalents adjusted for BSA [mg/m^2/day]) at Week 28, while Week 28 serum A4 is ≤120% of the baseline value or ≤ ULN, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5). For all subjects, baseline serum A4 will be defined as the average of all pre-morning glucocorticoid serum A4 values on Day 1 (for subjects who are <6 years of age or with a body weight <20 kg, only the single pre-morning glucocorticoid serum A4 value will be used). If values on Day 1 are missing, the last pre-morning glucocorticoid serum A4 value prior to Day 1 will serve as the baseline. The pre-morning glucocorticoid dose A4 value at Week 28 will be used for the comparison to the baseline A4 in assessing control (as defined above). Of note, 1 mg of methylprednisolone, prednisolone, or prednisone will be converted to 4 mg of hydrocortisone for the purpose of determining the hydrocortisone dose equivalents. The primary analysis of this endpoint will be performed using an ANCOVA model. The model will include treatment group, baseline

glucocorticoid daily dose, and stratification factors used in the randomization. This analysis will be performed using the FAS.

Subjects who have a decrease in glucocorticoid daily dose at Week 28 and who are not able to maintain their serum A4 at Week 28 at ≤120% of their baseline value or ≤ ULN for sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5) will be considered to have a zero percent change from baseline in the glucocorticoid daily dose at Week 28. Subjects who are missing glucocorticoid dose at Week 28, serum A4 levels at all time points at the Week 28 visit, or time point-matched serum A4 values at baseline and Week 28 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 any subject in the placebo treatment group. For subjects in the placebo treatment group, missing data will be imputed using observed data from any subject in the placebo treatment group.

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:

- The achievement of a reduction in glucocorticoid daily dose to physiologic levels (≤11 mg/m^2/day in hydrocortisone dose equivalent adjusted for BSA) at Week 28 while serum A4 is ≤120% of the baseline value or ≤ULN for sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5)
- Change from baseline in body mass index SDS at Week 28
- Change from baseline in mean 24-hour salivary 17-OHP at Week 28
- Acceptability and palatability of the study drug at Week 4

In the subgroup of subjects not at adult height, secondary endpoints will also include:

- Ratio of the change in bone age from baseline to Week 28 to the change in chronologic age from baseline to Week 28
- Change from baseline in Bayley-Pinneau predicted adult height SDS at Week 52

13.6.2. Safety Analyses

Safety data from the double-blind, placebo-controlled period through Week 28, the open-label treatment period through Week 52, and the OLE from Week 52 onwards will be analyzed separately. The subject incidence of TEAEs will be tabulated by randomized treatment group assignment at baseline for AEs, SAEs, fatal AEs, and AEs leading to discontinuation of study drug. Descriptive statistics by randomized treatment group assignment at baseline will be generated for additional safety data, including selected laboratory analytes, vital signs, ECG parameters, C-SSRS, and BPRS-c.

13.7. Week 28 Final Analysis

The final unblinded analysis of the double-blind, placebo-controlled period will be conducted once all subjects have had the opportunity to complete the Week 28 visit. Data through Week 28, including the primary and key 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 the analysis, the subject, investigator, all study center personnel, and Sponsor personnel with direct contact with the site (with the exception of clinical trial material supply chain personnel who are not involved in decisions regarding subject's treatment) will continue to be blinded to the subject's treatment assignment until unblinding will no longer jeopardize the integrity of the study (Section 10.7).

13.8. Week 52 Final Analysis

The final analysis of the open-label treatment period will be conducted once all subjects have had the opportunity to complete their Week 52 visit. At this time, all data collected from Week 28 to Week 52 will be analyzed.

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, competent (health) authority, or IRB/IEC representatives at any time. The investigator must agree to the inspection of study-related records by competent (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 acknowledgment 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, written informed consent from subject's parent(s) or legal guardian(s) with signed and witnessed study subject assent will be obtained (which may be done remotely, if allowed and remote consenting procedures are in place), as required by the governing IRB or ethics committee and according to local laws and regulations. Prior to any OLE-related study procedures, the subjects' parent(s) or guardian(s) (or the subject, if the subject has reached the age of majority) will review applicable portions of the ICF and subject will review applicable portion of the assent form (if applicable) and confirm whether the subject will participate in the optional OLE.

Each subject's chart will include the signed ICF with signed and witnessed study subject assent (or confirmation of verbal assent) for study participation. When the study treatment is completed and the eCRF has been monitored, the ICF and signed and witnessed study subject assent will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF and the signed and witnessed study subject assent in this central study folder.

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. As part of study-related monitoring, data audits, IRB/IEC review, and regulatory inspections, the investigator(s)/institution(s) will provide direct access to source data/documents.

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 the laws and regulations of the country in which the study is conducted. 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, national, and/or local 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. GLUCOCORTICOID STRESS DOSING GUIDANCE

Extra glucocorticoid (eg, hydrocortisone) must be given during times of **extreme physical stress** such as fever, vomiting and diarrhea, surgery, and significant trauma (eg, broken bones and concussions) (CARES Foundation, 2014; Miller et al., 2020; National Institutes of Health). The fludrocortisone dose does not need to be changed.

Type of Illness	Instruction
Minor illness or low-grade fever >100.5°F (38°C):	Double the hydrocortisone dose for the entire day, until fever or symptoms subside. Drink extra fluids (sugar- and salt-containing).
Moderate illness or fever ≥102°F (39°C)	Triple the hydrocortisone dose for the entire day (administered in 3 to 4 divided doses over the day) until fever or symptoms subside. Drink extra fluids (sugar- and salt-containing).
Vomiting	Triple the hydrocortisone dose. If vomiting occurs <30 minutes after taking the dose, wait 15 to 30 minutes and repeat the dose since it was likely not absorbed. If vomit again, administer injectable hydrocortisone (Solu-Cortef) (see below) and contact treating physician. Do not delay in giving injectable hydrocortisone.
Diarrhea	If no fever and feeling well, no need for stress dosing. If not feeling well, double the hydrocortisone dose. Drink extra fluids (sugar- and salt-containing).
All illnesses	To prevent dehydration, drink extra sugar and salt-containing fluids (eg, nondiet soda, Gatorade, popsicles, soup).
For minor surgical procedures not requiring general anesthesia	Triple the morning glucocorticoid dose.
Not tolerating oral medications or unconscious	Administer injectable (eg, intramuscular) hydrocortisone (Solu-Cortef) at 50 to 100 mg/m^2 or doses below and contact the treating physician. <3 years: 25 mg 3-12 years: 50 mg >12 years: 100 mg If unable to tolerate fluids or unconscious, contact emergency services for evaluation following injectable hydrocortisone treatment.

1. Signs of acute cortisol deficiency (adrenal crisis) include, but are not limited to: headache, nausea, vomiting, abdominal pain, dehydration, confusion, weakness, lethargy, pallor, fatigue, dizziness, hypotension, hypoglycemia.
2. Prevention of adrenal crisis: The injectable form of hydrocortisone (Solu-Cortef) must be kept at home and at school for emergencies. It may be kept in a medication cabinet for several years in the unmixed form. Check the expiration date and get a prescription refill when needed.
3. Call the treating physician for any of the following:
   a. Elevated temperature above 102□F (39□C)
   b. Fever for more than 3 days
   c. Difficulty waking your child
   d. Change in behavior such as acting confused
   e. Vomiting and unable to keep down medication
   f. Whenever hydrocortisone injection (Solu-Cortef) is given
4. Dexamethasone is not suitable for treatment of salt-wasting adrenal crisis because it has no mineralocorticoid effect. Methylprednisolone (10 to 25 mg/m2/dose) may be used to treat adrenal crisis although it has less mineralocorticoid activity than hydrocortisone. Hydrocortisone in high doses has mineralocorticoid effect, and thus no fludrocortisone is needed during intravenous stress dosing.

APPENDIX B. CRINECERFONT DOSE ADJUSTMENT GUIDANCE (AFTER MONTH 12/WEEK 52)

Guidance on changes to crinecerfont dosing in the OLE is provided in the table below.

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.

In the setting of inadequate efficacy (in the opinion of the investigator), 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 (ie, the evening dose has been doubled). 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. Changes to the crinecerfont dose (whether based on crossing into the next weight category or based on inadequate efficacy) should generally only be made at scheduled study visits.

Guidance for Dose Adjustment During the Open-Label Extension

Type of Change in Crinecerfont Dosing During OLE	Applicable Study Visits	Examples	Additional Guidance
Formulation switch: oral solution versus capsule, based on subject preference (only subjects receiving 50 mg bid or higher)	Month 12/Week 52	• 50 mg bid solution in core study but prefer capsule → switch to 50 mg bid capsule at Month 12.	• If there is a tolerability issue on the new formulation (eg, difficulty swallowing capsule), the subject can revert back to previous formulation (ideally within approximately 1 month). • Once formulation preference is established at or within approximately 1 month of Month 12, formulation should remain the same for the rest of the OLE. • The 25 mg bid dose regiment remains as solution (no option for 25 mg via capsule). • Change in formulation may occur in conjunction with weight-based adjustment or increase for inadequate efficacy.
Weight-based adjustment in dose when subject's body weight increases such that subject crosses into the next weight category 10 to <20 kg: 25 mg bid 20 to <55 kg: 50 mg bid ≥55 kg: 100 mg bid	Month 12/Week 52 and every 6 months thereafter during OLE	• 50 mg bid based on weight 20 to <55 kg in core study, which increases to ≥55 kg in OLE → adjust dose to 100 mg bid based on new weight category (even if efficacy assessed as inadequate at the same time).	• An increase in dose based on new weight category should be done first before increasing dose for inadequate efficacy if both conditions apply. • If weight decreases into a lower weight category, no dose adjustment is necessary unless there is a tolerability issue.
Dose increase for inadequate efficacy by doubling the evening dose • 25 mg bid → 25 mg qam, 50 mg qpm • 50 mg bid → 50 mg qam, 100 mg qpm • 100 mg bid → 100 mg qam, 200 mg qpm	Once per weight category starting at Month 12 and any subsequent visit during the OLE	• Inadequate efficacy at Month 12 on 50 mg bid and subject remains in the same weight category → increase to 50 mg qam, 100 mg qpm.	• If the crinecerfont dose is increased for inadequate efficacy, a study visit is performed approximately 1 month after dose increase for efficacy, PK, and safety assessments. • If there is a tolerability issue with the crinecerfont dose increase, the dose can be decreased back to prior dose. • If there is a need to decrease the crinecerfont dose back to the prior dose based on tolerability, the dose should not be increased again for inadequate efficacy during the rest of the OLE. • If subject weight crosses into the next weight category after increasing for inadequate efficacy, adjust the crinecerfont dose for weight first.

bid=twice daily; OLE=open-label extension; PK=pharmacokinetic; qam=in the morning, qpm=in the evening.