

**A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study
to Evaluate the Efficacy and Safety of SPR001 (Tildacerfont)
in Adult Subjects with Classic Congenital Adrenal Hyperplasia**

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SPR001-203
Spruce Biosciences, Inc.

CLINICAL STUDY PROTOCOL
Version 8.0, Dated 06 February 2024

SPONSOR APPROVAL PAGE

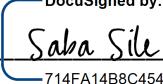
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Study Number: SPR001-203

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of SPR001 (Tildacerfont) in Adult Subjects with Classic Congenital Adrenal Hyperplasia

Study Number: SPR001-203

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I have reviewed the protocol and the attachments, and I agree to conduct this trial in accordance with all stipulations of the protocol, including all statements regarding confidentiality. I will ensure that no deviation from, or changes to, the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial participants or when change(s) involves only logistical or administrative aspects of the study.

I agree to conduct this trial in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP), the most recent version of the Declaration of Helsinki, and all applicable local and federal legal and regulatory requirements.

I agree to provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

I agree to permit periodic site monitoring of case report forms and source documents by the Sponsor or designee and by appropriate regulatory authorities.

I agree to supply the Sponsor with any information regarding ownership interest and financial ties with the Sponsor for the purpose of complying with regulatory requirements.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/EC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the consent form will be IRB/EC approved; a determination will be made regarding whether participants who provided previous consent need to be re-consented using the updated consent form.

Site Name: _____

Principal Investigator Name: _____

Investigator's Signature

Date

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LIST OF ABBREVIATIONS

17-OHP	17-hydroxyprogesterone
A4	androstenedione
ACTH	adrenocorticotropic hormone, corticotropin
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
C-SSRS	Columbia–Suicide Severity Rating Scale
CAH	congenital adrenal hyperplasia
CGI-I	Clinical Global Impression – Improvement Scale
CI	confidence interval
CMH	Cochran-Mantel-Haenszel (test)
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPK	creatinine phosphokinase
CRF	corticotropin-releasing factor
CRF ₁ , CRF ₂	corticotropin-releasing factor type-1 or type-2
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury

DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FCP	female of childbearing potential
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GC	glucocorticoid
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HC	hydrocortisone
HCe	hydrocortisone equivalent(s)
HDL	high-density lipoprotein
HEENT	head, eyes, ears, neck, and throat
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
HPA	hypothalamic-pituitary-adrenal
HPLC	high-performance liquid chromatography
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment (of acne severity)
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IQR	interquartile range
IRB	Institutional Review Board

ITT	Intent to Treat (Population)
IUD	intrauterine device
IUS	intrauterine system
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LH	luteinizing hormone
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mFG	modified Ferriman-Gallwey (score for hirsutism)
mitt	modified Intent to Treat (Population)
ms	millisecond
OTC	over the counter
PBPK	physiologically based pharmacokinetic (modeling)
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PP	Per Protocol (Population)
PRN	as needed
PRO	patient-reported outcome (measure)
PT	prothrombin time
PTT	partial thromboplastin time
PVC	polyvinyl chloride
PVDC	polyvinylidene chloride
QD	once daily
QoL	quality of life
QTcF	Fridericia-corrected QT interval
RBC	red blood cell
RTSM	randomization and trial supply management
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SF-36	Short Form 36
SGOT	serum glutamic-oxaloacetic transaminase

SGPT	serum glutamic-pyruvic transaminase
SHBG	sex hormone-binding globulin
SUSAR	suspected unexpected serious adverse reaction
TART	testicular adrenal rest tumor
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Study Number: SPR001-203
Study Title
A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of SPR001 (Tildacerfont) in Adult Subjects with Classic Congenital Adrenal Hyperplasia
Study Phase: IIb
Study Rationale
<p>Congenital adrenal hyperplasia (CAH) is a serious, chronically debilitating, and life-threatening genetic disorder characterized by impaired adrenal synthesis of cortisol and consequent overproduction of adrenal androgens. Cortisol deficiency disrupts the balance of the hypothalamic-pituitary-adrenal (HPA) axis by removing the negative feedback to the hypothalamus and pituitary provided by normal levels of cortisol. This leads to the compensatory hypersecretion of corticotropin-releasing factor (CRF) by the hypothalamus, overproduction of adrenocorticotrophic hormone (ACTH) by the pituitary gland, and consequent adrenal hyperplasia and overproduction of downstream adrenal hormones such as 17-hydroxyprogesterone (17-OHP) and androstenedione (A4), leading to androgen excess. Androgen excess may result in irregular menses, amenorrhea, hirsutism, and virilization in females; testicular adrenal rest tumors (TARTs) in males; and increased sebum production, acne, altered afternoon blood pressure profiles, and impaired fertility in either sex.</p> <p>The current standard of care for CAH is the long-term use of supraphysiologic levels of glucocorticoids (GCs) to replace the deficient cortisol and suppress androgen overproduction. This is a problematic therapy with significant side effects (e.g., loss of bone mineral density, iatrogenic Cushing's syndrome, metabolic disorders, and increased cardiovascular risk), a narrow therapeutic window, and overall poor treatment effectiveness. A non-steroidal treatment option that both controls androgen levels and reduces patient dependence on high-dose GCs would be of significant benefit to patients with CAH. Given the serious nature of CAH and the limitations and risks of chronic GC therapy, new treatments are urgently needed for patients with CAH.</p> <p>Tildacerfont, a potent and highly selective small-molecule antagonist of CRF type 1 (CRF₁) receptors in the pituitary gland, is being studied for the treatment of CAH on the basis of its ability to block the CRF signal produced by the hypothalamus, thereby decreasing ACTH overproduction by the pituitary and reducing excess accumulation of downstream adrenal hormones. This mechanism of action has been validated in CAH in earlier-phase clinical studies of tildacerfont. Given its mechanism of action, tildacerfont may enable a CAH patient to have normal androgen levels while taking GC at physiologic replacement levels.</p> <p>To date, tildacerfont has shown an acceptable safety profile at effective doses in nonclinical toxicology studies, Phase 1 clinical studies in healthy volunteers, and Phase 2 studies in adult subjects with classic CAH. Data from 2 previous Phase 2 studies demonstrated proof of concept for tildacerfont as a treatment for CAH, with meaningful reductions in ACTH (demonstrating target engagement) and</p>

<p>17-OHP and A4 (demonstrating efficacy in decreasing downstream adrenal hormones in CAH), and showed continued improvement in biomarker levels over a period of 12 weeks.</p> <p>In contrast to previously completed Phase 2 studies of tildacerfont, which were smaller, open-label, and shorter in duration, Study SPR001-203 is a larger, randomized, double-blind, placebo-controlled, dose-ranging study that will investigate the efficacy and safety of up to 70 weeks of treatment with tildacerfont in subjects with classic CAH who have elevated biomarkers at baseline on their current GC regimen. An optional Open-Label Extension Period will provide additional open-label treatment with tildacerfont at 200 mg QD for up to 240 weeks.</p>	
Objectives	Endpoints
Efficacy	
Primary Efficacy	
To evaluate the effect of tildacerfont in reducing A4 in subjects with classic CAH over 12 weeks	Assessment of dose response for change from baseline in log A4 after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
Secondary Efficacy	
To evaluate the effect of tildacerfont on A4 levels in subjects with classic CAH over 12 weeks	Change from baseline in A4 as assessed on the log scale after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing A4 in subjects with classic CAH over 12 weeks	Absolute change from baseline in A4 as determined via application of the delta theorem to the log scale analysis results after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing 17-OHP levels in subjects with classic CAH over 12 weeks	Assessment of dose response for change from baseline in log 17-OHP after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing 17-OHP in subjects with classic CAH over 12 weeks	Change from baseline in 17-OHP as assessed on the log scale after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing 17-OHP in subjects with classic CAH over 12 weeks	Absolute change from baseline in 17-OHP as determined via application of the delta theorem to the log scale analysis results after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
Exploratory Efficacy	
To evaluate the effect of tildacerfont in reducing A4 in subjects with classic CAH over 12 weeks	Proportion of subjects who achieve adequate control of A4 (A4 \leq 1x, 1.25x, 1.5x, 1.75x and 2x ULN) after 12 weeks on double-blind, placebo-controlled treatment (Week 18) for each treatment group

To evaluate the effect of tildacerfont in reducing 17-OHP in subjects with classic CAH over 12 weeks	Proportion of subjects who achieve adequate control of 17-OHP (17-OHP \leq 1200 ng/dL) after 12 weeks on double-blind, placebo-controlled treatment (Week 18) for each treatment group
To evaluate the effect of tildacerfont in reducing testicular adrenal rest tumor(s) (TART[s]) in male classic CAH subjects with TART(s) at baseline after 12 weeks on treatment	Change in the lesion volume of TART(s) from baseline after 12 weeks on double-blind, placebo-controlled treatment (Week 18) for each treatment group
To characterize dose-exposure of Tildacerfont in CAH	Correlation of Tildacerfont plasma concentration vs dose
To evaluate the effect of tildacerfont on biomarkers relative to each other in subjects with classic CAH over 12 weeks	Estimate the within subject correlation of A4 and 17-OHP log scale values over time
To evaluate the effect of tildacerfont in improving QoL in subjects with classic CAH	Change from baseline at Week 76 in SF-36 total score across all ITT subjects
To evaluate the effect of tildacerfont in improving acne in classic CAH subjects with acne at baseline	Change from baseline at Week 76 in Investigator's Global Assessment (IGA) score of acne severity score across all ITT subjects with acne at baseline
To evaluate the effect of tildacerfont in improving hirsutism in female classic CAH subjects with hirsutism at baseline	Change from baseline at Week 76 in Modified Ferriman-Gallwey (mFG) score for hirsutism across all female ITT subjects with hirsutism at baseline
To evaluate the proportion of subjects who can reduce GC use in subjects with classic CAH	Proportion of subjects with at least a 5 mg/day hydrocortisone equivalents (HCe) reduction from baseline in GC dose and A4 \leq ULN at Week 76
To evaluate the effect of tildacerfont in reducing TART(s) in male classic CAH subjects with TART(s) at baseline	Change in the total lesion volume of TART(s) from baseline at Week 76 across all male ITT subjects with TART(s) at baseline
To evaluate the effect on tildacerfont in reducing A4 in subjects with classic CAH over 12 weeks	Assessment of dose response for change from baseline in log ATCH after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing ACTH in subjects with classic CAH over 12 weeks	Absolute change from baseline in ACTH as determined via application of the delta theorem to the log scale analysis results after 12 weeks on double-blind, placebo-controlled treatment (Week 18)

To evaluate the effect of tildacerfont in reducing ACTH in subjects with classic CAH over 12 weeks	Change from baseline in ACTH as assessed on the log scale after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To characterize dose-exposure of Tildacerfont in CAH	Estimate the within subject correlation of A4 and 17-OHP log scale values with tildacerfont plasma concentrations over time
<i>Exploratory Efficacy (Optional Open-Label Extension Period)</i>	
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels in subjects with CAH	Proportion of subjects with GC dose \leq 25 mg/day in HCe and A4 \leq ULN at end of treatment (EOT)
To evaluate the percentage change in GC use in subjects with CAH	Percent change from baseline in GC dose at EOT
To evaluate the effect of tildacerfont in reducing cardiovascular risk in subjects with CAH and at least one cardiovascular risk factor at baseline	Proportion of subjects with improvement in at least one cardiovascular risk factor at EOT
To evaluate the effect of tildacerfont in reducing TART(s) in male CAH subjects with TART(s) at baseline	Proportion of male subjects with reduction in TART(s) at EOT who had TART(s) at baseline
Safety	
To evaluate the safety of tildacerfont in subjects with CAH	Adverse events (AEs), serious adverse events (SAEs)
Study Design	
This is a study with a 3-part treatment period that will evaluate the efficacy and safety of up to 70 weeks of treatment with tildacerfont in subjects with classic CAH who have elevated biomarkers at baseline. An optional Open-Label Extension Period will provide additional open-label treatment with tildacerfont at 200 mg QD for up to 240 weeks.	
Refer to the study schematic provided in Section 1.2 .	
Study Periods	
This study will consist of the following periods:	
<ul style="list-style-type: none">• A \leq45-day <i>Screening Period</i> for confirmation of eligibility<ul style="list-style-type: none">○ Optional A4 Screening Visit○ Screening information captured within 45 days of Day 1 in this study (particularly screening information transferred from Spruce Biosciences Study SPR001-204) will be used to determine eligibility and fulfill screening requirements for this study.	

- A 6-week, single-blind, placebo *Run-in Period*, during which subjects will be assessed for adherence to their existing GC therapy and daily ingestion of placebo with food
- Subjects who continue to meet all eligibility criteria at the end of the Run-in Period will then enter a 3-part *Treatment Period*:
- **Part A:** The first 12 weeks of the Treatment Period will be a randomized, double-blind, placebo-controlled, dose-ranging study. Subjects will be randomized in a 1:1:1:1 ratio to receive either placebo or tildacerfont at a dose of 50 mg once daily (QD), 100 mg QD, or 200 mg QD.
- **Part B:** During the second 12 weeks of the Treatment Period, all subjects will receive active drug (tildacerfont), with possible dose escalation for eligible subjects. Subjects and Investigators will remain blinded to previous treatment in Part A and dose level of tildacerfont in Part B.
 - Subjects who were randomized to placebo in Part A will receive tildacerfont at 100 mg QD at the beginning of Part B.
 - Subjects who were randomized to tildacerfont at 200 mg QD in Part A will continue to receive tildacerfont at 200 mg QD in Part B.
 - Subjects who were randomized to tildacerfont at 50 mg QD or 100 mg QD in Part A will continue to receive the same dose at the beginning of Part B if they have A4 ≤ULN at Week 18. These subjects will be escalated to the next highest dose at the beginning of Part B if they have A4 >ULN at Week 18 (i.e., subjects previously on 50 mg QD would be escalated to 100 mg QD, and subjects previously on 100 mg QD would be escalated to 200 mg QD).
- Based on the results of the Week 24 visit of Part B, subjects will have another opportunity for tildacerfont dose escalation if they have A4 >ULN and are tolerating their current dose of tildacerfont. Specifically:
 - Subjects currently taking 50 mg QD will be escalated to 100 mg QD.
 - Subjects currently taking 100 mg QD will be escalated to 200 mg QD.
- **Part C:** During the last 46 weeks of the Treatment Period, all subjects will be escalated to 200 mg QD, with periodic opportunities for GC adjustment for eligible subjects. Subjects and Investigators will continue to remain blinded to previous treatment in Part A and dose level of tildacerfont in Part B.
 - Subjects with A4 ≤ULN at Week 38 or Week 46 will begin to reduce their daily GC dose level by increments of approximately 5 mg/day HCe each time, down to a minimum of 15 mg/day HCe (see [Section 6.5.1.4](#)).
- For subjects continuing into the optional Open-Label Extension Period
 - The Open-Label Extension Period will provide subjects with up to 240 weeks of treatment with tildacerfont 200 mg QD.
 - Subjects will be eligible to adjust GC dose level at each visit (see [Section 6.5.1.4](#)).
- A 30-day *Follow-up Period at EOT*

- Subjects who do not continue to the Open-Label Extension Period upon completion of Treatment Period Part C will enter a 30-day Follow-up Period.
- Upon completion of the Open-Label Extension Period, subjects will enter a 30-day Follow-up Period.
- At the end of study treatment, subjects will maintain the GC regimen and mineralocorticoid regimen (as applicable) established during the course of the study until the 30-day follow-up visit unless the Investigator determines that the subject's clinical status necessitates a dosing change. After completion of the study, GC therapy will be managed at the discretion of the subject's treating physician.

Changes in GC dosing are generally not permitted during this study except in Part C, in the Open-Label Extension Period, and in the case of stress dosing throughout the study. During times of clinically significant physical stress such as intercurrent illness with fever, surgical procedures, or significant trauma, stress dosing with extra GC (in the form of hydrocortisone [HC]) for prevention of adrenal crisis will be allowed according to "sick day guidelines" (see [Section 6.5.1.5](#)).

Study Visit Schedule

- During the Screening Period:
 - Optional A4 Screening Visit
 - Screening Visit at \leq 45 days before Day 1
- During the Run-in Period: visits at Day 1 and Week 4; scheduled telephone contact at Week 2
- During the Treatment Period:
 - Part A: visits every 4 weeks, at Week 6 (baseline) and Weeks 10, 14, and 18; scheduled telephone contact at Week 8
 - Part B: visits every 6 weeks, at Weeks 24 and 30; scheduled telephone contact at Week 21
 - Part C: visits every 6 to 12 weeks, at Weeks 38, 46, 58, 70, and 76; scheduled telephone contact at Week 52
- During the optional Open-Label Extension Period: Visits every 3 to 6 months at Weeks 88, 100, 124, 148, 172, 196, 220, 244, 268, 292 and 316
- At 30 days after the last dose of study drug for final safety follow-up
- As-needed (PRN) telephone contacts are detailed under [Telephone Contacts](#).

Mode of Study Visits in the Context of Coronavirus Disease 2019 (COVID-19) or Other Logistical Challenges

All efforts should be made to conduct all visits in the clinic as per the Principal Investigator's clinical judgement or patient's preference. Since the COVID-19 pandemic is expected to continue during the conduct of this trial, study visits can be adapted into a combination of in-clinic and telemedicine activities, with optional at-home visits, to mitigate the risk of COVID-19 infection associated with study participation and to accommodate local and individual circumstances while maintaining participant access to healthcare resources.

The clinic activities of the Screening Visit may be conducted remotely (at the subject's home) if approved by the site's Institutional Review Board (IRB)/Ethics Committee (EC).

The electronic data capture (EDC) system will capture the mode by which data are collected for each visit/activity.

If home visits are conducted, the qualified medical professionals who will perform the study's home visits are defined as individuals who meet national/local licensing requirements needed to perform the procedures required at the home visits. Their national/local licensure will be verified, and they will complete training on the study protocol and Good Clinical Practice (GCP). If the medical professional does not meet the national/local licensing requirements needed to perform the optional home visit activities (physical examination, acne IGA score, and hirsutism mFG score for females), the Investigator or Investigator-delegated study personnel must complete these activities for each visit.

Refer to [Section 11](#) for more information on study conduct in the context of COVID-19 or other logistical challenges.

Telephone Contacts

Sites will make scheduled telephone contacts to all subjects at Weeks 2, 8, 21, and 52 to record any AEs and concomitant medications. During the Week 2 telephone contact, sites will also confirm subject adherence to study activities.

After receiving A4 results, sites will make telephone contacts to applicable subjects concerning tildacerfont dose escalation or GC adjustment.

- For subjects who are eligible for GC adjustment following the Week 38 and/or 46 study visits as well as visits in the optional Open-Label Extension Period, sites will contact these subjects by telephone within 2 weeks after the applicable study visit. The site will direct a subject to reduce his/her GC dose at that time if the subject has not experienced any change in clinical status since the previous study visit. If no GC dose adjustment is warranted based on the A4 level, the site does not need to contact the subject. If a subject's GC dose is adjusted, the site will telephone the subject again 7 days after the dose adjustment to assess for the occurrence of AEs and the initiation of new concomitant medications.

Subjects should be instructed to telephone sites if they have any concerns about their health.

PRN telephone contacts initiated by sites and telephone contacts initiated by subjects should be captured in the EDC system as "unscheduled" telephone contacts.

Study Diary/Drug Adherence Data Collection

During the Run-in and Treatment Periods, subjects will use an electronic study diary to document study drug and background GC adherence through Week 18. Female subjects will also use the study diary to record menstrual information (including start and stop dates of menses) across the full treatment period up to Week 76.

Study Population

This study will randomize approximately 72 subjects with classic CAH currently receiving GC therapy into the start of the Treatment Period. The study will enroll subjects at approximately 130 investigative sites globally.

Eligibility Criteria

Inclusion Criteria

1. Male and female subjects ≥ 18 years old at screening
2. Has a known childhood diagnosis of classic CAH due to 21-hydroxylase deficiency based on genetic mutation in *CYP21A2* and/or documented (at any time) elevated 17-OHP and currently treated with HC, HC acetate, prednisone, prednisolone, methylprednisolone (or a combination of the aforementioned GCs)
3. Has been on a stable, supraphysiologic dose of GC replacement (defined as ≥ 15 mg/day and ≤ 60 mg/day in HCe) for ≥ 1 month before screening
4. Has A4 $>$ ULN at both screening and Week 4 (measured before any AM GC dose) if daily GC dose <30 mg OR has A4 >2.5 x ULN at both screening and Week 4 (measured before any AM GC dose)
5. For subjects with the salt-wasting form of CAH, subject has been on a stable dose of mineralocorticoid replacement for ≥ 1 month before screening
6. Agrees to follow contraception guidelines ([Section 5.2.5](#)). Male subjects must also agree to refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug.
7. Is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Exclusion Criteria

1. Has a known or suspected diagnosis of any other known form of classic CAH (not due to 21-hydroxylase deficiency)
2. Has a history that includes bilateral adrenalectomy or hypopituitarism
3. Has a history of allergy or hypersensitivity to tildacerfont, any of its excipients, or any other CRF₁ receptor antagonist
4. Current treatment with dexamethasone as GC therapy for CAH
 - a. Prior treatment with dexamethasone is allowed as long as the transition to an alternative GC regimen (eg, HC, prednisone, or prednisolone) has resulted in a stable dose of GC replacement for ≥ 1 month before screening.
5. Is not adherent to GC or study drug dosing regimen during the Run-in Period (defined as taking $<80\%$ of expected doses based on drug accountability)
6. Shows clinical signs or symptoms of adrenal insufficiency
7. Has had a clinically significant unstable medical condition, medically significant illness, or chronic disease occurring within 30 days of screening, including but not limited to:
 - a. An ongoing malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
 - b. Estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m²
 - c. Current or history of liver disease (with the exception of Gilbert's syndrome).
 - d. History of alcohol or substance abuse within the last year, or any significant history of alcohol or substance abuse that would likely prevent the subject from reliably participating in the study, based on the opinion of the Investigator
 - e. Active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening

- f. Subjects who plan to undergo bariatric surgery during the study are excluded.
- g. Any other condition that would impact subject safety or confound interpretation of study results
- 8. Psychiatric conditions, including but not limited to bipolar disorder, schizophrenia, or schizoaffective disorders that are not effectively controlled on medication and may have an adverse impact on study compliance. Symptoms including hallucinations, delusions, and psychosis are exclusionary. Additionally:
 - a. Increased risk of suicide based on the Investigator's judgment or the results of the Columbia–Suicide Severity Rating Scale (C-SSRS) conducted at screening and Week 6 (eg, C-SSRS Type 3, 4, or 5 ideation within the past 6 months or any suicidal behavior within the past 12 months)
 - b. Hospital Anxiety and Depression Scale (HADS) score >12 for either depression or anxiety at screening or Week 6
- 9. Has clinically significant abnormal electrocardiogram (ECG) or clinical laboratory results. Abnormal results that must be reviewed and discussed with the Medical Monitor to determine eligibility for this study include but are not limited to:
 - a. Any clinically meaningful abnormal ECG results, including Fridericia-corrected QT interval (QTcF) >450 milliseconds (ms) for male participants or >470 ms for female participants
 - b. Alanine aminotransferase (ALT) >2x ULN
 - c. Total bilirubin >1.5x ULN
 - d. Total bile acids >5x ULN
- 10. Routinely works overnight shifts
- 11. Subjects with travel plans/work schedules that result in significant and frequent changes in time zones (>2 hours) will require Medical Monitor approval for enrollment.
- 12. Females who are pregnant or nursing
- 13. Use of any other investigational drug from 30 days or 5 half-lives (whichever is longer) before screening to the end of the study
- 14. Use of the following drugs from 30 days or 5 half-lives (whichever is longer) before Day 1 to the end of the study:
 - a. Rosiglitazone, aromatase inhibitors, testosterone, growth hormones, or any other medication or supplement that could impact subject safety or confound interpretation of study results
 - b. The drugs listed in [Section 13.1](#), which are:
 - i. Moderate to strong inhibitors and/or inducers of cytochrome P450 3A4 (CYP3A4)
 - ii. Sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 (except hormonal contraception containing ≤35 µg ethinyl estradiol)
 - iii. Sensitive substrates or narrow-therapeutic-range substrates of breast cancer resistance protein (BCRP) (except those that can be administered QD in the morning, separated by approximately 10 hours from evening administration of study drug)

15. Donation or receipt of blood from 90 days before Screening to the end of the study; donation or receipt of platelets, white blood cells, or plasma from 30 days before Screening to the end of the study

Investigational Drug

The drug product is a small-molecule CRF₁ receptor antagonist and will be supplied as yellow, round, convex tablets containing 50 mg of drug substance.

Placebo will be supplied as tablets that look identical to drug product but contain no drug substance.

Dose, Route, Regimen

Subjects will use their own physician-prescribed supply of GCs as prescribed during the study, including during the Run-in Period.

Subjects will take placebo (during the Run-in Period) or assigned study drug (during the Treatment Period) orally each day between 6 PM and midnight, with an evening meal. The evening meal should contain approximately 25- 50% fat content. Study drug may be consumed up to 30 minutes after completing the evening meal, if necessary.

During Part A (the first 12 weeks of the Treatment Period), subjects will be randomized in a 1:1:1:1 ratio to receive either placebo or tildacerfont at a dose of 50 mg QD, 100 mg QD, or 200 mg QD.

During Part B (the second 12 weeks of the Treatment Period) and Part C (the last 46 weeks of the Treatment Period), all subjects will receive active drug (tildacerfont).

- Subjects who were randomized to placebo in Part A will receive tildacerfont 100 mg QD at the beginning of Part B.
- Subjects who were randomized to tildacerfont 200 mg QD in Part A will continue to receive tildacerfont at 200 mg QD throughout Parts B and C.
- Based on A4 results at Weeks 18 and 24 study visits, eligible subjects may undergo a tildacerfont dose escalation after each of these study visits. Specifically:
 - Subjects taking tildacerfont 50 mg QD will either continue to receive the same dose (if A4 \leq ULN) or be escalated to tildacerfont 100 mg QD (if A4 >ULN and the subject is tolerating his/her current tildacerfont dose)
 - Subjects taking tildacerfont 100 mg QD will either continue to receive the same dose (if A4 \leq ULN) or be escalated to tildacerfont 200 mg QD (if A4 >ULN and the subject is tolerating his/her current tildacerfont dose).
- At Week 30, all subjects will be escalated to 200 mg QD.

Immediately following the Weeks 18 and 24 visits, subjects will continue to take their previously assigned study drug until A4 laboratory results are received, the randomization and trial supply management (RTSM) system determines the appropriate tildacerfont doses for the next portion of the study, and subjects receive their tildacerfont doses for the next portion of the study.

During the optional Open-Label Extension Period, subjects will continue to receive tildacerfont at 200 mg QD.

On the evenings before scheduled laboratory assessments, subjects should take their evening GC dose before 10 PM. On the mornings of scheduled laboratory assessments, subjects should delay taking any

morning dose of GC medication until after the 8 AM (± 1 hour) laboratory assessments have been completed. On all other days during the study, subjects should take their GC medication at the usual time(s). Mineralocorticoid may be taken at any time of day, but its timing relative to laboratory assessments should be consistent throughout the study.

During times of clinically significant physical stress such as intercurrent illness with fever, surgical procedures, or significant trauma, stress dosing with extra GC (in the form of HC) for prevention of adrenal crisis will be allowed according to “sick day guidelines” (see [Section 6.5.1.5](#)). The Sponsor will provide GC for periods of stress dosing.

Study drug will be discontinued in subjects who meet individual treatment-stopping criteria (see [Section 7.1](#)).

Study Duration

The expected duration of study participation for each subject is up to approximately 86 weeks. This includes a Screening Period of ≤ 45 days, a placebo Run-in Period of 6 weeks, a Treatment Period of 70 weeks, and a safety follow-up period of approximately 30 days. Subjects who continue in the optional Open-Label Extension Period will participate for up to an additional 240 weeks.

Statistical Analyses

Statistical Hypotheses

For the Primary Efficacy Analysis, the null hypothesis is that there is no difference in the profile of log A4 change from baseline through 12 weeks of blinded randomized treatment between tildacerfont and placebo. The alternative hypothesis is that there is difference in the profile of log A4 change from baseline through 12 weeks of blinded randomized treatment between tildacerfont and placebo.

Sample Size

A sample size of n=15 subjects per group will provide at least 80% power to detect a difference of at least 50% in A4 mean percent change from baseline between a given dose level of tildacerfont and placebo, assuming a common standard deviation (SD) of 30%.

An assumed dropout rate of 15% during the Treatment Period results in a target of 18 subjects per group and a total sample size of 72 subjects who enter the Treatment Period.

Analysis Populations

- The Intent-to-Treat (ITT) Population will include all randomized subjects regardless of treatment period eligibility or completion.
- The Modified ITT (mITT) Population is defined as all randomized subjects who receive at least 1 dose of study drug (tildacerfont or placebo), have at least 1 post-baseline A4 assessment, and did not change background GC through Week 18.
- The Per Protocol (PP) Population for each part of the Treatment Period will include all eligible subjects who have no major protocol deviations that would affect the analysis of efficacy data.
- The Safety Population will include all subjects who receive at least 1 dose of study drug (tildacerfont or placebo) during the Treatment Period.
- The Pharmacokinetics (PK) Population will include all randomized subjects who receive at least 1 dose of tildacerfont and have at least 1 evaluable PK sample.

Refer to [Section 9.3](#) for further information on analysis populations.

General Statistical Considerations

Continuous data will be summarized using an 11-point descriptive summary (n, mean, SD, median, interquartile range [IQR; 25% quartile, 75% quartile], minimum, and maximum, geometric mean, geometric coefficient of variance [CV%], 95% confidence interval [CI] for geometric mean [including geometric mean ratio and its 95% CI]) or 8-point descriptive summary (n, mean, SD, median, Q1, Q3, minimum, and maximum). Categorical data will be summarized using the frequency of events and percentage of total events.

For missing data, a retrieved dropout approach will be used in which missing endpoint data for subjects who discontinued early will be imputed using data collected from subjects after discontinuation of study drug

Efficacy Analyses

All efficacy analyses will be conducted on the ITT Population using a 2-sided alpha of 0.05.

The primary objective of the study is to evaluate the effect of tildacerfont in controlling A4 levels in adult subjects with classic CAH who have elevated biomarkers at baseline on their current dose of GC replacement therapy over the 12-week, double-blind, placebo-controlled Part A of the Treatment Period. This objective will be achieved via A4 dose response analysis. Statistical testing for dose response will be performed using the repeated measures random coefficients mixed-effects model.

The secondary efficacy analyses related to A4 will be achieved as an integral part of the dose response modelling. The secondary efficacy analyses related to 17-OHP will be conducted using the same methodology as the primary efficacy analysis.

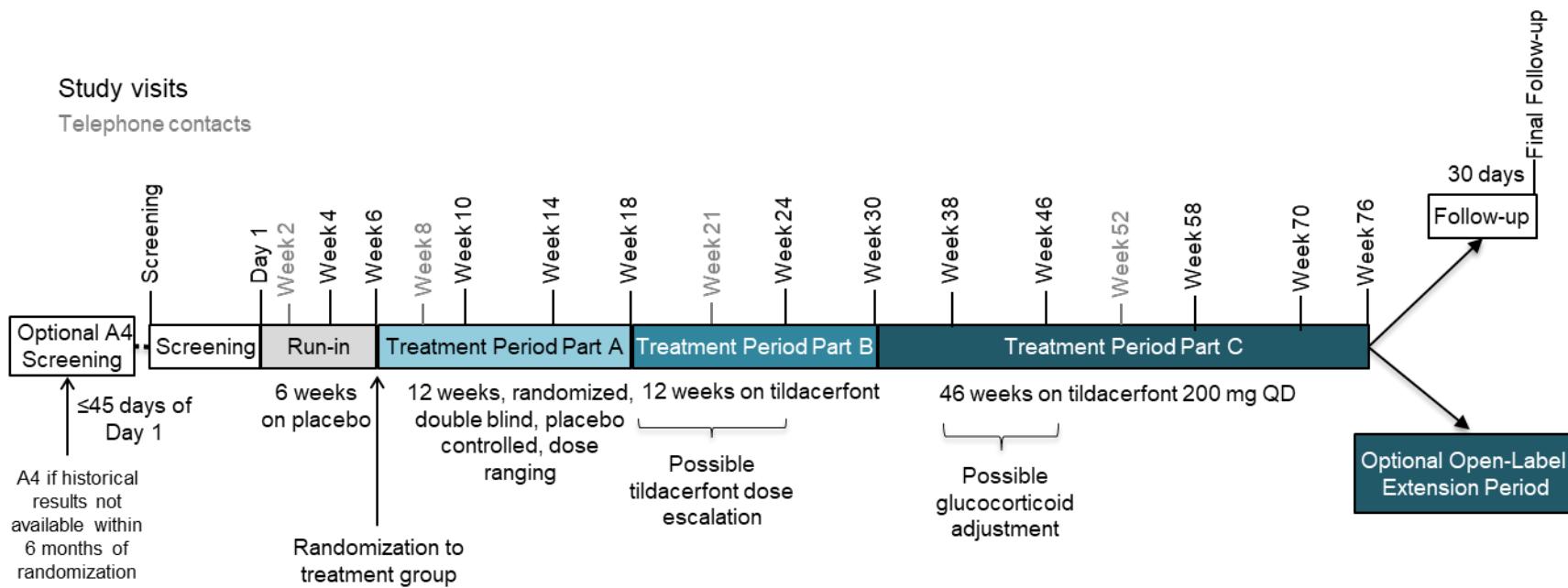
Quality-of-life endpoints, IGA acne score, mFG hirsutism score, and TART lesion size will be analyzed using a repeated measure mixed effects model with treatment and visit as fixed effects, subject as a random effect, and the baseline score as a covariate if >2 timepoints are assessed. If only the baseline timepoint and a single post-baseline timepoint are assessed for the endpoint, an analysis of covariance (ANCOVA) model with the baseline score as a covariate will be used. There will be no imputation of missing data.

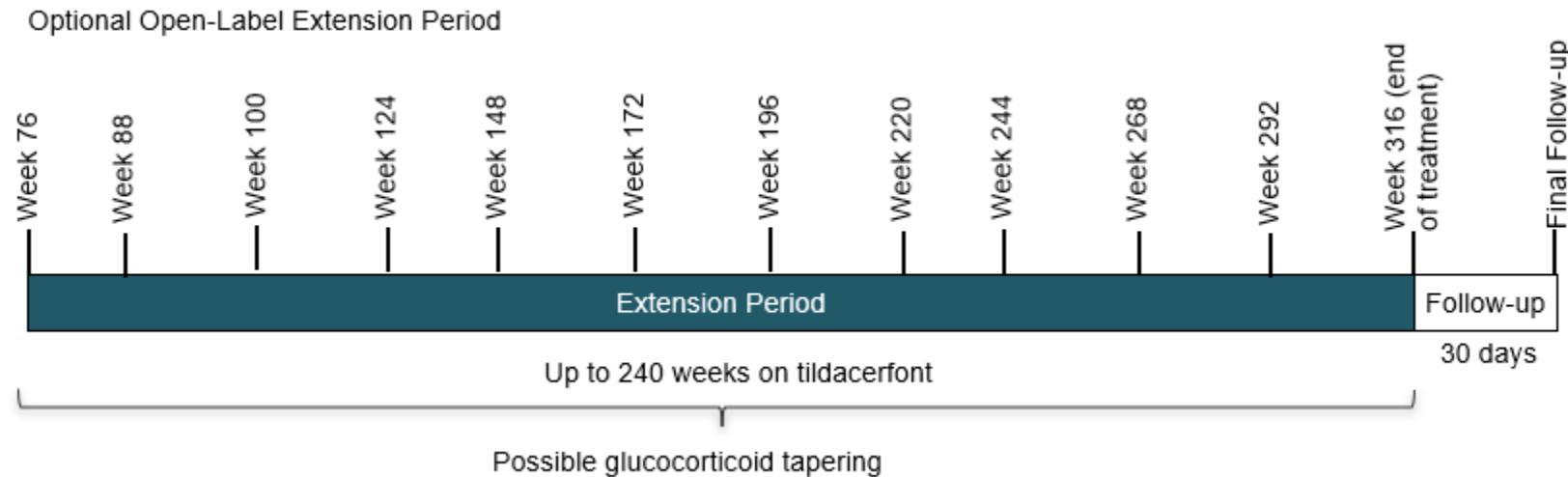
Endpoints during the optional Open-Label Extension Period will be summarized descriptively.

Safety Analyses

Safety analyses will be conducted on the Safety Population. All safety data will be presented in listings. Summary tables will be provided for concomitant medications, AEs, hematology and chemistry laboratory results, vital signs, and ECG findings. Safety data will be summarized by treatment group using frequency of event or descriptive statistics, as appropriate.

1.2 Schema





1.3 Schedules of Activities

1.3.1 Optional A4 Screening Visit

For subjects with unknown A4 levels, prior to a morning GC dose, an optional A4 Screening Visit may be conducted up to 45 days prior to Day 1 to test A4 levels prior to further screening evaluations. An informed consent form (ICF) specific to this visit will be signed by the subject. Retesting of A4 levels will not be required at the SPR001-203 Screening Visit if eligible A4 results have been obtained within 45 days prior to the Day 1 visit.

1.3.2 Schedule of Screening Activities

Screening will be conducted in-clinic. Some activities of the Screening Visit may be conducted remotely (at the subject's home) if approved by the site's IRB/EC. Screening activities to be performed at the subject's home will be conducted after activities to be performed in the clinic for each study visit. On the evening before screening laboratory samples will be collected, subjects should take their evening GC dose before 10 PM. Screening laboratory samples will be collected at 8 AM (± 1 hour), after the subject has fasted overnight (nothing to eat after midnight), and before the subject takes any morning dose of GC medication.

Screening information from the parallel Spruce Biosciences Study SPR001-204 may be used to determine eligibility and fulfill screening requirements for this study if the information was captured within 45 days before Day 1 in this study.

STUDY VISIT NUMBER	Screening Period	
	1a Optional A4 Screening	1b Screening
STUDY DAY	In-Clinic Screening Visit	In-Clinic Screening Visit
Informed consent	X	X
Inclusion/exclusion criteria		X
Demography		X
Medical history		X
Prior medications from past year		X
Concomitant medications		X
Prior and current GC regimens ²		X
Vital signs ³ , body weight		X
Height		X
Full physical examination		X
C-SSRS		X
HADS		X
Hepatitis B & C and HIV tests		X ⁴

STUDY VISIT NUMBER	Screening Period	
	1a Optional A4 Screening	1b Screening
	In-Clinic Screening Visit	In-Clinic Screening Visit
STUDY DAY	≤45 days before Day 1 ¹	≤45 days before Day 1 ¹
Urine drug screen		X ⁴
Serum pregnancy test for FCP		X ⁴
Hormones from blood	X ⁵	X ^{4, 6}
Clinical laboratory ⁷		X ⁴
Urinalysis		X ⁴
HbA1c		X ⁴
12-lead ECG		X ⁴
Report subject's status to site		X ⁴

Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotrophic hormone; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C-SSRS, Columbia–Suicide Severity Rating Scale; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FCP, female of childbearing potential; FSH, follicle-stimulating hormone; GC, glucocorticoid; GGT, gamma-glutamyl transferase; HADS, Hospital Anxiety and Depression Scale; HbA1c, hemoglobin A1c; HCe, hydrocortisone equivalents; HIV, human immunodeficiency virus; INR, international normalized ratio; LH, luteinizing hormone; PT, prothrombin time; PTT, partial thromboplastin time; SHBG, sex hormone–binding globulin.

¹ Screening information captured within 45 days of the start of Day 1 in this study (particularly screening information transferred from Spruce Biosciences Study SPR001-204) will be used to determine eligibility and fulfill screening requirements for this study.

² Subjects must be on a stable, supraphysiologic dose of GC replacement (defined as ≥15 and ≤60 mg HCe per day) for ≥1 month before the Screening Visit. Information to be collected at screening about a subject's current and historical GC therapy during the past year include the type(s) of GC, the regimen(s), reason(s) that the subject is/was on a particular GC regimen, and any GC stress dosing during the past year.

³ Vital signs consist of systolic and diastolic blood pressure, pulse rate, body temperature, and respiration rate and will be measured after a 5-min rest period.

⁴ These clinic activities of the Screening Visit may be conducted remotely (at the subject's home) if approved by the site's IRB/EC.

⁵ A4 and 17-OHP will be measured. The blood draw for the A4 and 17-OHP sample will be obtained at 8 AM (± 1 hour) prior to a morning GC dose.

⁶ A4, 17-OHP, ACTH, and testosterone will be measured prior to a morning GC dose.

⁷ Clinical laboratory assessments include hematology, clinical chemistry (including liver function tests such as ALT, AST, ALP, GGT, bilirubin, and total bile acids), coagulation (PT/INR and PTT), lipid panel, thyroid panel, LH, FSH, SHBG, renin, aldosterone, inhibin B for males only, and estradiol, prolactin, and progesterone for females only. eGFR for screening will be calculated from blood creatinine measured as part of screening clinical chemistry.

1.3.3 Schedule of Post-Screening Activities

	Placebo Run-in Period			Treatment Period															Follow- up ¹	ET
				Part A					Part B				Part C							
	2	3	4 Base line	5	6	7	8	9	10	11	12	13	14	15						
STUDY VISIT NUMBER																			STUDY DAY ³	
STUDY WEEK	0	2	4	6	8	10	14	18	21	24	30	38	46	52	58	70	76 ²	80	Last dose +30 days	
STUDY DAY ³	1	15	29	43	57	71	99	127	148	169	211	267	323	365	407	491	533			
Study Visit (V)/ Telephone Contact (T) ⁴	V	T	V	V	T	V	V	V	T	V	V	V	V	T	V	V	V	V	STUDY DAY ³	
Urine pregnancy test for FCP	X		X	X		X	X	X		X	X	X	X		X	X	X	X	STUDY DAY ³	
Hormones from blood ^{5,6}	X		X	X		X	X	X		X	X	X	X		X	X	X	X <th>STUDY DAY³</th>	STUDY DAY ³	
Clinical laboratory ^{5,7}			X		X	X	X			X	X	X	X		X	X	X	X <th>STUDY DAY³</th>	STUDY DAY ³	
Urinalysis ⁵				X				X									X		STUDY DAY ³	
HbA1c, fasting glucose and insulin, HOMA-IR ⁵				X				X									X	X	STUDY DAY ³	
PK ^{5,8}				X		X		X					X				X	X	STUDY DAY ³	
Genetic sample ⁹				X															STUDY DAY ³	
Vital signs ¹⁰ , body weight	X		X	X		X	X	X		X	X	X	X		X	X	X	X <th>STUDY DAY³</th>	STUDY DAY ³	
Waist circumference				X				X									X		STUDY DAY ³	
12-lead ECG				X				X			X						X	X	STUDY DAY ³	
HADS				X				X			X				X	X	X		STUDY DAY ³	
SF-36	X			X				X									X		STUDY DAY ³	
PGIC								X									X		STUDY DAY ³	
Scrotal ultrasound for males			X ¹¹					X ¹²									X ¹²		STUDY DAY ³	
Inclusion/exclusion criteria ¹³				X															STUDY DAY ³	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	STUDY DAY ³		
GC monitoring ¹⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	STUDY DAY ³		

	Placebo Run-in Period	Treatment Period															Follow- up ¹	ET	
		Part A					Part B				Part C								
STUDY VISIT NUMBER	2		3	4 Base line	5	6	7		8	9	10	11		12	13	14	15		
STUDY WEEK	0	2	4	6	8	10	14	18	21	24	30	38	46	52	58	70	76 ²	80	
STUDY DAY ³	1	15	29	43	57	71	99	127	148	169	211	267	323	365	407	491	533	Last dose +30 days	
Study Visit (V)/ Telephone Contact (T) ⁴	V	T	V	V	T	V	V	V	T	V	V	V	T	V	V	V	V		
C-SSRS				X				X			X						X	X	
CGI-I								X									X	X	
Randomization to treatment in Part A ¹⁵ /Determination of tildacerfont dose in Parts B and C ¹⁶				X				X		X	X								
Dispense study drug ¹⁷	X			X		X	X	X ^{18,19}		X ^{18,19}	X ²⁰	X	X		X	X ²⁰			
Study drug accountability			X	X		X	X	X		X	X	X	X		X	X	X	X	
Dispense HC for stress dosing and perform accountability ²¹	X		X	X		X	X	X		X	X	X	X		X	X	X	X	
PRN telephone contact to follow up after possible tildacerfont dose escalation ²²										X	X								
PRN telephone contacts regarding GC adjustment ²³												X	X						
Review study diary/drug adherence ²⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination ²⁵	X		X	X		X	X	X		X	X	X	X		X	X	X	X	
Acne IGA score ²⁶				X			X									X		X	
Hirsutism mFG score for females ²⁶				X			X									X		X	

Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotrophic hormone; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CGI-I, Clinical Global Impression – Improvement Scale; C-SSRS, Columbia–Suicide Severity Rating Scale; EC, Ethics Committee; ECG, electrocardiogram; EDC, electronic data capture; ET, early termination; FCP, female of childbearing potential; FSH, follicle-stimulating hormone; GC, glucocorticoid; GGT, gamma-glutamyl transferase; HADS, Hospital Anxiety and Depression Scale; HbA1c, hemoglobin A1c; HC(e), hydrocortisone (equivalents); HIV, human immunodeficiency virus; HOMA-IR, homeostatic model assessment of insulin resistance; IGA, Investigator's Global Assessment (score for acne); INR, international normalized ratio; IRB, Institutional Review Board; LH, luteinizing hormone; mFG, modified Ferriman-Gallwey (score for hirsutism); PGIC, Patient Global Impression of Change; PK, pharmacokinetics; PRN, as needed; PROs, patient-reported outcome measures; PT, prothrombin time; PTT, partial thromboplastin time; RTSM, randomization and trial supply management (system); SF-36, Short Form 36; SHBG, sex hormone-binding globulin; T, telephone contact; TART, testicular adrenal rest tumor; V, study visit.

Footnotes from 1.3.3 Schedule of Post-Screening Activities:

¹ Subjects who do not continue to the optional Open-Label Extension Period upon completion of Treatment Period Part C will enter a 30-day Follow-up Period.

² For subjects who continue to the optional Open-Label Extension Period, Week 76 will be considered Study Visit Number 1 for optional Open-Label Extension Period.

³ All study visits and telephone contacts should be performed on the indicated study days. In cases where adherence to the foregoing schedule is not possible, all activities for study visits and telephone contacts after the Week 0 visit must be completed within a ± 3-day window after the indicated study days.

⁴ During scheduled telephone contacts, sites will record any AEs and concomitant medications. After receiving A4 results, sites will make telephone contacts to applicable subjects concerning study drug dose escalation and GC adjustment (detailed later in this Schedule of Post-Screening Activities). Subjects should be instructed to telephone sites if they have any concerns about their health. PRN telephone contacts initiated by sites and telephone contacts initiated by subjects should be captured in the EDC system as “unscheduled” telephone contacts.

⁵ Samples for these lab assessments will be obtained at 8 am (± 1 hour), after an overnight fast (nothing to eat after midnight), and before any morning dose of GC medication. On the evenings before scheduled laboratory assessments, subjects should take their evening GC dose before 10 pm.

⁶ A4, 17-OHP, ACTH, and testosterone will be measured.

⁷ Clinical laboratory assessments include hematology, clinical chemistry (including liver function tests such as ALT, AST, ALP, GGT, bilirubin, and total bile acids), coagulation (PT/INR, and PTT), lipid panel, thyroid panel, LH, FSH, SHBG, renin, aldosterone, inhibin B for males only, and estradiol, prolactin, and progesterone for females only.

⁸ A single blood sample will be drawn for PK measurement at each specified study visit.

⁹ Where local regulations permit and subject to discretionary approval from each site's IRB/EC and to subject consent, a voluntary blood sample may be collected for DNA analysis. See [Section 13.4](#) for specifics on genetic testing that may be performed.

¹⁰ Vital signs consist of systolic and diastolic blood pressure, pulse rate, body temperature, and respiration rate and will be measured after a 5-min rest period.

¹¹ The initial scrotal ultrasound can be performed anytime during screening up to Week 4 of run-in and will be considered the baseline measurement for TART.

¹² Scrotal ultrasounds will only be conducted in subjects who had TART(s) at baseline.

¹³ If a subject fails to meet eligibility criteria during or at the end of the Run-in Period, the investigational site will schedule an abbreviated early termination visit to review AEs and concomitant medications and perform an abbreviated physical examination (preferably in the clinic, but also permissible via home visit).

¹⁴ Subjects must be on a stable regimen of GC replacement ≥ 15 and ≤ 60 mg HCe per day throughout the Run-in Period, Part A, and Part B. Subjects will confirm whether their GC regimen was followed each day in a study diary. On the evenings before scheduled laboratory assessments, subjects should take their evening GC dose before 10 pm. On the mornings of scheduled laboratory assessments, subjects should delay taking any morning dose of GC medication until after the laboratory assessments have been completed.

¹⁵ In Part A, subjects will be randomized to tildacerfont 50 mg QD, tildacerfont 100 mg QD, tildacerfont 200 mg QD, or placebo.

¹⁶ In Parts B and C, all subjects will receive tildacerfont. Subjects who were randomized to placebo in Part A will receive tildacerfont 100 mg QD at the beginning of Part B. Subjects who were randomized to tildacerfont 200 mg QD in Part A will continue to receive tildacerfont 200 mg QD throughout Parts B and C. Based on A4 results from the Weeks 18 and 24 study visits, eligible subjects may undergo a tildacerfont dose escalation after each of these study visits. Specifically, subjects taking tildacerfont 50 mg QD will either continue to receive the same dose (if A4 \leq ULN) or be escalated to tildacerfont 100 mg QD (if A4 $>$ ULN and the subject is tolerating his/her current tildacerfont dose); subjects taking tildacerfont 100 mg QD will either continue to receive the same dose (if A4 \leq ULN) or be escalated to tildacerfont 200 mg QD (if A4 $>$ ULN and the subject is tolerating his/her current tildacerfont dose). At Week 30, all subjects will be escalated to 200 mg QD.

¹⁷ Either the subject will pick up study drug in the clinic or the study drug will be shipped directly to the subject. Study drug will be taken daily between 6 pm and midnight, with an evening meal. The evening meal should contain approximately 25-50% fat content. Study drug may be consumed up to 30 minutes after completing the evening meal, if necessary.

¹⁸ Immediately following each indicated study visit, subjects will continue to take their previously assigned study drug until subjects receive their tildacerfont doses for the next portion of the study.

¹⁹ IRT order assigned to specific participant. The shipment does not need to be accepted in IRT. Blister Cards will be assigned when the "Confirm A4 Value" action is recorded for Week 18 and week 24.

²⁰ IRT order assigned to specific participant. The shipment does not need to be accepted in IRT. Blister Cards will be assigned when the "Record Study Visit" action is recorded for Week 30 - Week 70 since no A4 value is needed to determine the dose at these visits.

²¹ Bottles of HC for stress dosing (see [Section 6.5.1.5](#)) will be dispensed starting at Day 1 and thereafter as needed to replace opened bottles. Accountability for HC will be performed at every study visit.

²² For subjects who are eligible for blinded tildacerfont dose escalation following the indicated study visits (i.e., subjects with A4 $>$ ULN who have not reduced GC), the site will telephone the subject again 7 days after the dose adjustment to assess for the occurrence of AEs and the initiation of new concomitant medications. Subjects who were not eligible for study drug dose escalation will not be telephoned.

²³ In Part C, subjects with A4 \leq ULN at Week 38 or Week 46 will begin to adjust their daily GC dose level by increments of approximately 5 mg/day HCe each time, down to a minimum of 15 mg/day HCe. Sites will contact subjects who are eligible for a GC adjustment by telephone within 2 weeks after each applicable study visit. Subjects who are not eligible for a GC adjustment will not be telephoned. The site will direct the subject to adjust his/her GC dose at that time if the subject has not experienced any change in clinical status since the previous study visit. If a subject's GC dose is adjusted, the site will telephone the subject again 7 days after the dose adjustment to assess for the occurrence of AEs and the initiation of new concomitant medications.

²⁴ Subjects will use an electronic study diary to document study drug and background GC adherence through Week 18. Female subjects will also use the study diary to record menstrual information (including start and stop dates of menses) across the full treatment period up to Week 76.

²⁵ A full physical examination will be conducted at Day 1, Week 18, and Week 76. The full physical examination may exclude rectal, genitourinary, and breast exams. An abbreviated physical examination will be conducted at all other visits indicated. If the physical exam is performed at the subject's home, the qualified medical professional will report any changes to the subject's health to the site to determine whether further evaluation is needed via an unscheduled visit.

²⁶ At Week 6, acne will be evaluated in all subjects and hirsutism in all female subjects. After Week 6, acne/hirsutism will only be evaluated in subjects who had acne/hirsutism at Week 6.

1.3.4 Schedule of Optional Open-Label Extension Period Activities

	Extension Treatment Period ¹												Follow-up	ET
	2	3	4	5	6	7	8	9	10	11	12	13		
STUDY VISIT NUMBER	88	100	124	148	172	196	220	244	268	292	316	320		
STUDY WEEK	617	701	869	1037	1205	1373	1541	1709	1877	2046	2213	Last dose +30 days		
STUDY DAY ¹	V	V	V	V	V	V	V	V	V	V	V	V		
Study Visit (V)	X	X	X	X	X	X	X	X	X	X	X	X	V	
Urine pregnancy test for FCP														X
Hormones from blood ^{2,3}	X	X	X	X	X	X	X	X	X	X	X			X
Clinical laboratory ²	X	X	X	X	X	X	X	X	X	X	X			X
Vital signs ⁴ , body weight, waist circumference	X	X	X	X	X	X	X	X	X	X	X			X
SF-36			X		X		X		X		X			X
C-SSRS ⁵			X		X		X		X		X			X
Scrotal ultrasound for males ⁶			X		X		X		X		X			X ⁶
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X		X
Review adverse events	X	X	X	X	X	X	X	X	X	X	X	X		X
Abbreviated physical examination			X		X		X		X		X			X
Dispense study drug ⁷	X	X	X	X	X	X	X	X	X	X	X			
Study drug accountability	X	X	X	X	X	X	X	X	X	X	X			X
GC dose adjustment telephone contacts ⁸	X	X	X	X	X	X	X	X	X	X	X			
Dispense HC for stress dosing and perform accountability ⁹	X	X	X	X	X	X	X	X	X	X	X			X

Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; C-SSRS, Columbia–Suicide Severity Rating Scale; ET, early termination; FCP, female of childbearing potential; GC, glucocorticoid; HC(e), hydrocortisone (equivalents); SF-36, Short Form 36; V, study visit

Footnotes from 1.3.4 Schedule of Optional Open-Label Extension Period Activities:

¹ For subjects who continue to the optional Open-Label Extension Period, Week 76 visit (as reflected in Table 1.3.3) will be considered as Study Visit 1 for the optional Open-Label Extension Period and will be performed within \pm 3-day window. All visits starting Week 88 should be performed within a +30-day window.

² Samples for these lab assessments will be obtained at 8 AM (\pm 1 hour), after an overnight fast (nothing to eat after midnight) and before any morning dose of GC medication. On the evenings before scheduled laboratory assessments, subjects should take their evening GC dose before 10 PM.

³ A4 and 17-OHP and testosterone will be measured.

⁴ Vital signs consist of systolic and diastolic blood pressure, pulse rate, body temperature, and respiration rate and will be measured after a 5-min rest period.

⁵ SF-36 and C-SSRS are paper based during the optional Open-Label Extension Period.

⁶ Scrotal ultrasounds will only be conducted in subjects who had TART(s) at baseline.

⁷ Subject will pick up study drug in the clinic. Study drug will be taken daily between 6 PM and midnight, with an evening meal. The evening meal should contain approximately 25–50% fat content. Study drug may be consumed up to 30 minutes after completing the evening meal, if necessary.

⁸ During the Treatment Period, sites will make telephone contacts to subjects who are eligible for a GC dose adjustment within 2 weeks after each applicable study visit and based on their A4 level at that visit. Subjects who are not eligible for a GC change will not be telephoned. The site will direct the subject to adjust his/her GC dose by approximately 5 mg/day HCe increments if the subject has not experienced any change in clinical status since the previous study visit. If a subject's GC dose is adjusted, the site will telephone the subject again 7 days after the GC dose adjustment to assess for the occurrence of AEs and the initiation of new concomitant medications. GC dose may be reduced to a minimum of 15 mg HCe per day (approximately physiologic replacement level).

⁹ Bottles of HC for stress dosing (see [Section 6.5.1.5](#)) will be dispensed as needed. Accountability for bottles of HC will be performed at every study visit.

2 INTRODUCTION

2.1 Study Rationale

CAH is a serious, chronically debilitating, and life-threatening genetic disorder characterized by impaired adrenal synthesis of cortisol and overproduction of adrenal androgens. Cortisol deficiency disrupts the balance of the HPA axis by removing the negative feedback to the hypothalamus and pituitary provided by normal levels of cortisol. This leads to the compensatory hypersecretion of CRF by the hypothalamus, overproduction of ACTH by the pituitary gland, and consequent adrenal hyperplasia and overproduction of downstream adrenal hormones such as 17-OHP and A4, leading to androgen excess. Androgen excess may result in irregular menses, amenorrhea, hirsutism, and virilization in females; TARTs in males; and increased sebum production, acne, altered afternoon blood pressure profile, and impaired fertility in either sex.

The current standard of care for CAH is the long-term use of supraphysiologic levels of GCs to replace the deficient cortisol and suppress androgen overproduction. This is a problematic therapy with significant side effects (eg, loss of bone mineral density, iatrogenic Cushing's syndrome, metabolic disorders, and increased cardiovascular risk), a narrow therapeutic window, and overall poor treatment effectiveness. A non-steroidal treatment option that both controls androgen levels and reduces patient dependence on high-dose GCs would be of significant benefit to patients with CAH. Given the serious nature of CAH and the limitations and risks of chronic GC therapy, new treatments are urgently needed for patients with CAH.

Tildacerfont, a potent and highly selective small-molecule antagonist of CRF₁ receptors in the pituitary gland, is being studied for the treatment of CAH on the basis of its ability to block the CRF signal produced by the hypothalamus, thereby decreasing ACTH overproduction by the pituitary and reducing excess accumulation of downstream adrenal hormones. This mechanism of action has been validated in CAH in earlier-phase clinical studies of tildacerfont. Given its mechanism of action, tildacerfont has the potential to effect normalization of androgen levels while allowing for GC replacement at physiologic dose levels.

To date, tildacerfont has shown an acceptable safety profile at effective doses in nonclinical toxicology studies, Phase 1 clinical studies in healthy volunteers, and Phase 2 studies in adult subjects with classic CAH. Data from 2 previous Phase 2 studies demonstrated proof of concept for tildacerfont as a treatment for CAH, with meaningful reductions in ACTH (demonstrating target engagement) and 17-OHP and A4 (demonstrating efficacy in decreasing downstream adrenal hormones in CAH), and showed continued improvement in biomarker levels over a period of 12 weeks.

In contrast to previously completed Phase 2 studies of tildacerfont, which were smaller, open-label, and shorter in duration, Study SPR001-203 is a larger, randomized, double-blind, placebo-controlled, dose-ranging study that will investigate the efficacy and safety of up to 70 weeks of treatment with tildacerfont in subjects with classic CAH who have elevated biomarkers at baseline. An optional Open-Label Extension Period will provide additional open-label treatment with tildacerfont at 200 mg QD for up to 240 weeks.

2.2 Background

2.2.1 Congenital Adrenal Hyperplasia

CAH is a serious and chronically debilitating autosomal recessive genetic disorder characterized by impaired adrenal synthesis of the corticosteroids, cortisol and aldosterone and consequent overproduction of adrenal androgens ([Merke and Bornstein 2005](#)). Approximately 95% of CAH patients have a mutation in the *CYP21A2* gene, which encodes the cytochrome P450c21 enzyme, commonly known as 21-hydroxylase ([Arlt 2010](#); [Speiser 2018](#)). Mutations in other genes that encode enzymes critical in adrenal steroidogenesis (*CYP17A1*, *HSD3B2*, *CYP11B1*, and *POR*) contribute to the remaining approximately 5% of CAH cases ([Turcu and Auchus 2015](#)). 21-hydroxylase catalyzes the conversion of progesterone to 11-deoxycorticosterone (a precursor to aldosterone) and the conversion of 17-OHP to 11-deoxycortisol (the precursor to cortisol) ([White and Speiser 2000](#); [Bachelot 2008](#); [Doleschall 2014](#); [Auchus 2015](#)). A deficiency in 21-hydroxylase thus results in a critical blockade in the adrenal steroid synthesis pathways that produce cortisol (and aldosterone in some individuals) and an accumulation of the precursors to these steroids (mostly 17-OHP, since accumulating progesterone is converted to 17-OHP). These steroid precursors are then diverted into the synthetic pathway for adrenal androgens, resulting in overproduction of A4 and downstream adrenal androgens.

Impaired cortisol production also disrupts the balance of the HPA axis by removing the negative feedback to the hypothalamus and pituitary gland provided by normal levels of cortisol. This leads to the compensatory hypersecretion of CRF by the hypothalamus and overproduction of ACTH by the pituitary. High levels of ACTH stimulate the adrenal gland to produce even greater quantities of 17-OHP, A4, and downstream adrenal androgens, resulting in adrenal hyperplasia.

The clinical manifestations of CAH are the direct result of cortisol and aldosterone deficiencies and of androgen overproduction ([Merke and Bornstein 2005](#); [Arlt 2010](#); [Reisch 2019](#)). Cortisol deficiency can result in adrenal insufficiency and life-threatening adrenal crises. Overproduction of adrenal androgens may result in advanced skeletal maturation, diminished height potential, premature pubarche, and precocious puberty in children; irregular menses, amenorrhea, hirsutism, and virilization in females; TARTs in males; and increased sebum production, acne, altered afternoon blood pressure profiles, and impaired fertility in either sex.

CAH is typically classified as either classic (the more severe form that usually presents with adrenal crisis in infancy or virilization during early childhood) or nonclassic (the milder form that may not become evident until later childhood or early adulthood). Classic CAH can be further sub-classified as salt-wasting or simple virilizing. Approximately 75% of classic CAH patients have the salt-wasting form of CAH characterized by the loss of large amounts of sodium via urine (hyponatremia), hyperkalemia, and elevated plasma renin activity indicating hypovolemia, leading to dehydration and hypotension that can be life threatening in early infancy ([Speiser 2018](#)). Salt-wasting CAH is caused by severe aldosterone deficiency resulting from severe mutations that completely ablate 21-hydroxylase activity. Milder mutations that result in even 1% to 2% residual 21-hydroxylase activity enable sufficient aldosterone production to avoid neonatal adrenal crisis and produce the simple virilizing form of CAH in the remaining 25% of CAH patients.

Numerous studies have documented diminished quality of life in patients with CAH ([Han 2013](#); [Aulinas and Webb 2014](#); [Gilban 2014](#); [Hummel 2016](#)). CAH patients commonly experience sleep disturbances, concentration problems, and challenges with social interactions ([Malouf 2010](#)). Severe fatigue is experienced by nearly half of CAH patients ([Giebels 2014](#)), and diminished memory performance has also been reported ([Browne 2015](#)). Psychiatric disorders and substance-use disorders are common, particularly among those with the most severe genotype ([Engberg 2015](#)). Faced with the debilitating effects of the disease itself, ineffective treatment, and/or the severe side effects of long-term high-dose GC treatment, CAH patients may develop depression and anxiety. Patients with CAH have increased mortality, with one study documenting a mean age of death of 41.2 years in patients with 21-hydroxylase deficiency, 6.5 years earlier than matched controls ([Falhammar 2014](#)). The causes of death were adrenal crisis (42%), cardiovascular disease (32%), cancer (16%), and suicide (10%).

Refer to the Investigator's Brochure (IB) for additional information on CAH.

2.2.2 Current Treatment for CAH

There are no approved therapies for CAH. The current standard of care for CAH is lifelong treatment with GCs (eg, HC, prednisone, prednisolone, dexamethasone) to replace cortisol and suppress adrenal androgen overproduction ([Speiser 2018](#)). In patients with salt-wasting CAH, mineralocorticoids (eg, fludrocortisone) are also used to replace aldosterone; before weaning, NaCl supplements are also provided to prevent a potentially lethal salt-losing crisis ([Padidela and Hindmarsh 2010](#)). Evidence-based treatment guidelines for CAH are only beginning to be developed ([Reisch 2015](#); [Speiser 2018](#)), and current overall treatment effectiveness for CAH patients is poor ([Mnif 2012](#); [Bachelot 2015](#)).

Treatment of CAH with chronic GCs is a problematic therapy with a narrow therapeutic window and significant side effects. The challenge in using GC therapy to manage CAH lies in striking the difficult balance between hyperandrogenism and hypercortisolism ([Merke 2008](#); [Arlt 2010](#); [Reisch 2019](#)). Treating CAH patients with lower, physiologic doses of GC (≤ 10 mg/m² of HCe per day, [Lukert 2006](#)) may be sufficient to prevent adrenal insufficiency but does not suppress androgen overproduction. Hyperandrogenic sequelae include hirsutism, female virilization, TARTs, acne, and infertility ([Merke 2008](#); [Reisch 2019](#)). In contrast, treating patients with higher, supraphysiologic doses of GCs may suppress androgen overproduction but often results in iatrogenic hypercortisolism. Hypercortisolism leads to bone loss, Cushing's syndrome, metabolic disorders and increased cardiovascular risk (hypertension, greater body mass index [BMI], obesity, hypercholesterolemia, insulin resistance), psychological and cognitive changes, musculoskeletal effects, gastrointestinal (GI) effects, and other effects ([Merke 2008](#); [Moghadam-Kia and Werth 2010](#); [Reisch 2019](#)). Thus, the ideal dose, which reduces excess androgen without supplying excess GC, is often difficult to find in the individual patient, and patients often experience hyperandrogenism, hypercortisolism, or a combination of these states ([Falhammar 2007](#); [Merke 2008](#)). Despite the availability of GCs as a treatment for CAH, approximately two-thirds of CAH patients are considered outside the acceptable bounds of biochemical control based on 17-OHP and A4 levels ([Han 2014](#)). Among patients with 21-hydroxylase deficiency treated with GCs, normal serum A4 has been shown to be achieved in only 36% of patients ([Arlt 2010](#)).

Over a lifetime, the treatment of patients with CAH shifts from an emphasis on normal childhood growth to pubertal development to adult fertility and long-term health concerns, including metabolic abnormalities, cardiovascular disease, osteoporosis, and overall diminished quality of life (Arlt 2010; Auchus 2015).

Given the serious nature of CAH and the lack of satisfactory available therapies, new treatments are urgently needed for patients with CAH.

2.2.3 Tildacerfont for the Treatment of CAH

Tildacerfont is an oral small-molecule antagonist of the CRF₁ receptors on the pituitary gland. In vitro studies show that tildacerfont binds to CRF₁ receptors with high affinity and specificity and blocks CRF-stimulated receptor function. In CAH, tildacerfont is intended to block the CRF signal produced by the hypothalamus, thereby decreasing CRF₁ receptor-mediated ACTH overproduction by the pituitary and reducing excessive accumulation of downstream adrenal hormones such as 17-OHP and A4. This mechanism of action has been validated in CAH in earlier-phase clinical studies of tildacerfont (see [Section 2.2.5](#)). Given its mechanism of action, tildacerfont may enable a CAH patient to have normal androgen levels while taking GC at physiologic replacement levels.

Nonclinical studies of tildacerfont are summarized in [Section 2.2.4](#). Clinical experience with tildacerfont is summarized in [Section 2.2.5](#).

2.2.4 Nonclinical Studies of Tildacerfont

A comprehensive nonclinical development program has been conducted to support clinical development of tildacerfont.

In vitro membrane- and cell-based radioligand binding assays have demonstrated that tildacerfont is a potent CRF₁ receptor antagonist that is highly selective for the human CRF₁ over the human CRF₂ receptor (6.1 nM vs >100 nM, respectively) and inhibits CRF-stimulated human CRF₁ receptor function.

Nonclinical safety pharmacology studies have indicated no undesirable pharmacodynamics (PD) effects of tildacerfont on physiological functions.

Nonclinical PK studies have shown tildacerfont to be quickly absorbed; distributed primarily to endocrine, fatty, metabolic/excretory, and GI tract tissues and not to melanin-containing tissues; metabolized primarily by CYP3A4; and eliminated to below the quantitation limit in most tissues by 168 hours, with the majority of drug substance eliminated from tissues by 72 hours. Refer to [Section 6.5.2](#) for information on potential drug interactions of tildacerfont.

Nonclinical toxicology studies to date include completed genotoxicity studies and adult, juvenile, and reproductive and developmental toxicology studies.

- In a standard battery of genotoxicity studies, tildacerfont was found to be neither mutagenic nor clastogenic/aneuploid.
- Chronic repeat-dose toxicity studies have been conducted in adult rats and dogs using the clinically relevant route (oral) and schedule (daily) of administration. Tildacerfont doses of up to 2000 mg/kg/day have been evaluated in rats and dogs dosed for up to 13 weeks, doses of up to 1000 mg/kg/day have been evaluated in rats dosed for 26 weeks, and doses of up to

1000/500 mg/kg/day have been evaluated in dogs dosed for 39 weeks. Target organs identified histopathologically in rats and/or dogs include the liver, testes/epididymides, and thyroid gland. Refer to [Section 2.3.1](#) for a discussion of the potential liver, testicular, and thyroid risks associated with tildacerfont.

- In developmental toxicity studies in juvenile rats administered tildacerfont doses of up to 1000 mg/kg/day for 7 weeks beginning on postnatal day 45 (comparable to a 12-year-old human), adverse effects were limited to microscopic findings in the testes of males at 1000 mg/kg/day, consistent with the findings in adult rats.
- In reproductive and developmental toxicity studies, no adverse effects on fertility, early embryonic development, embryo-fetal development, or maternal toxicity were noted in rats at tildacerfont doses \leq 1000 mg/kg/day. In rabbits, maternal toxicity was observed at \geq 30 mg/kg/day, and embryo-fetal developmental toxicity was observed at \geq 100 mg/kg/day.

Refer to the IB for additional information on nonclinical studies of tildacerfont.

2.2.5 Clinical Experience with Tildacerfont

Tildacerfont has been studied in 7 completed interventional clinical studies to date, of which 5 were Phase 1 studies and 2 were Phase 2 studies.

To date, tildacerfont has been well tolerated at effective doses with no related SAEs. Two subjects in Phase 2 studies experienced transient elevations in liver function tests (LFTs) after being administered doses higher than those in this study (see [Section 2.3.1](#) for more details).

Proof of concept for tildacerfont as a CRF₁ receptor antagonist in CAH patients was demonstrated in the Phase 2 Study SPR001-201, which showed clinical evidence of CRF₁ receptor target engagement (reductions in ACTH) and reductions in key adrenal hormones (17-OHP and A4) at multiple dose levels tested. In addition, the Phase 2 Study SPR001-202 showed tildacerfont's ability to normalize ACTH and adrenal hormones with 12 weeks of treatment at a dose of 400 mg QD (see [Section 2.3.2](#) for more details).

2.3 Risk/Benefit Assessment

2.3.1 Observed Potential Risks

2.3.1.1 Liver

Effects on the liver noted in chronic toxicity animal studies include the following:

- Increased liver weight (in female rats dosed with 1000 mg/kg/day [\sim 39-fold higher exposure in rat than the expected average exposure at the highest human dose in this study] for 26 weeks)
- Hepatocellular hypertrophy (in rats dosed with \leq 1000 mg/kg/day [\sim 39-fold higher] for 26 weeks and in dogs dosed with \leq 1000/500 mg/kg/day [$>$ 66-fold higher exposure in dog than the expected average exposure at the highest human dose in this study] for up to 39 weeks)
- Increased liver mRNA expression of CYP2B1 and CYP2B2 (in rats dosed with 300 and 1000 mg/kg/day [$>$ 11-fold higher exposure in rat than the expected average exposure at the highest

human dose in this study] for 26 weeks) or of CYP1A1, CYP2B11, and CYP3A12 (in dogs dosed with $\leq 1000/500$ mg/kg/day [>66 -fold higher] for up to 39 weeks)

- Hepatocellular degeneration, focal necrosis, vacuolation, bile duct hyperplasia, and/or periportal mixed leukocyte infiltration associated with increases in gamma-glutamyl transferase (GGT) and ALT activities (in dogs dosed with 300 and 1000/500 mg/kg/day [>39 -fold higher exposure in dog than the expected average exposure at the highest human dose in this study] for up to 39 weeks)

Reversible effects on LFTs have been observed in the Phase 2 clinical studies. Two subjects in Cohort A of Study SPR001-201 experienced transient elevations in ALT and aspartate aminotransferase (AST) after receiving 1000 mg QD for 2 weeks (following 2 weeks on 200 mg QD and 2 weeks on 600 mg QD). One subject experienced an ALT elevation of up to 8.6x ULN, and the other subject experienced a mild ALT elevation of 2.3x ULN. Concurrent elevations in AST were also observed to a lesser extent in these subjects, while bilirubin levels remained within normal limits. Both events resolved spontaneously within 2 to 4 weeks without any specific medical management. Both subjects were subsequently re-challenged with tildacerfont. The first subject was re-challenged in Study SPR001-202 at 400 mg QD, experienced a moderate increase in ALT (2.9x ULN), and was subsequently discontinued from that study. The other subject was re-challenged in Cohort B of Study SPR001-201 at 200 mg twice daily (BID) and did not experience a recurrence of any liver enzyme elevation.

No treatment-emergent LFT abnormalities were observed in the Phase 1 studies, which treated healthy adults with single tildacerfont doses of up to 800 mg and multiple tildacerfont doses of up to 200 mg QD for 14 days. No LFT abnormalities have been observed in CAH subjects treated with tildacerfont doses of ≤ 200 mg QD for 2 weeks in the Phase 2 studies.

2.3.1.2 Testicular

Reversible testicular/spermatocyte degeneration/atrophy was consistently observed in chronic toxicity studies: in rats and dogs dosed with 2000 mg/kg/day (~ 79 -fold [rat] and >200 -fold [dog] higher exposure than the expected average exposure at the highest human dose in this study) for 13 weeks, in rats dosed with ≤ 1000 mg/kg/day (~ 39 -fold higher) for 26 weeks, and in dogs dosed with 1000/500 mg/kg/day (>66 -fold higher) for <20 weeks. Effects included smaller testes and/or epididymides, seminiferous tubule degeneration/atrophy, and germ cell debris and/or reduced sperm in epididymides. However, male reproductive studies in rats showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day [~ 39 -fold higher]). Additionally, no meaningful effects on clinical laboratory markers of testicular function (luteinizing hormone [LH], follicle-stimulating hormone [FSH], inhibin B, and sex hormone-binding globulin [SHBG]) have been observed in male subjects in the Phase 1 or Phase 2 clinical studies.

2.3.1.3 Thyroid

Effects on the thyroid gland noted in chronic toxicity studies include increased weight of the thyroid/parathyroid gland (in rats dosed at ≤ 1000 mg/kg/day [~ 39 -fold higher exposure in rat than the expected average exposure at the highest human dose in this study] for 26 weeks), C-cell adenoma of the thyroid (in male rats dosed at 1000 mg/kg/day [~ 39 -fold higher] for 26 weeks), and follicular hypertrophy (in dogs dosed at 2,000 mg/kg/day [~ 262 -fold higher] for 13 weeks). The follicular hypertrophy was considered secondary to the hepatocellular hypertrophy also noted in these animals and not a direct result of tildacerfont administration. Thyroid follicular cell hypertrophy can be

associated with increased functional hepatocellular mass, with increased thyroxine metabolism and increased release of thyroid-stimulating hormone (TSH) from the pituitary. The clinical relevance of this secondary finding is presently unclear. Thyroid function was not evaluated in the Phase 1 studies, and no meaningful changes in thyroid function have been observed in the Phase 2 studies.

2.3.2 Observed Potential Benefits

Evidence from nonclinical and available clinical data suggests that tildacerfont is effective as a CRF₁ receptor antagonist.

Data from Study SPR001-201 (which tested tildacerfont doses of 200 mg QD, 600 mg QD, 1000 mg QD, 100 mg BID, and 200 mg BID, all for 2 weeks) showed clinical evidence of CRF₁ receptor target engagement and reductions in key adrenal hormones in adult subjects with classic CAH. For example, after 2 weeks of treatment at a total daily dose of 200 mg, subjects with elevated ACTH at baseline had a mean reduction in ACTH of approximately 33%, and subjects with elevated biomarkers at baseline had mean reductions in both 17-OHP and A4 of 13%. The higher total daily doses evaluated in Study SPR001-201 demonstrated similar efficacy, suggesting that a total daily dose of 200 mg may be at the top of the dose-response curve.

Data from Study SPR001-202 (which tested a tildacerfont dose of 400 mg QD for 12 weeks) demonstrated continued improvement in ACTH, 17-OHP, and A4 levels over 12 weeks of treatment. Subjects with elevated biomarkers at baseline had a maximum mean percentage reduction of 68% in ACTH, 88% in 17-OHP, and 81% in A4 over 12 weeks of treatment; individual maximum reductions exceeded 97% for all of these biomarkers. Additionally, 67% of subjects with abnormal ACTH at baseline achieved normalization of ACTH on study, and 40% of subjects with abnormal A4 at baseline achieved normalization of A4 on study.

2.3.3 Assessment of Potential Risks and Benefits

Multiple study design elements have been incorporated to mitigate the potential risks of LFT laboratory abnormalities, testicular injury, and thyroid effects described in [Section 2.3.1](#). First, these risks are all associated with higher doses of tildacerfont; in this study, tildacerfont tablets will be administered at a range between 50 mg and 200 mg QD, lower than the doses at which elevated LFTs have been observed and doses that have been well tolerated. Additionally, clinical laboratory measures of liver chemistry, testicular function, and thyroid function will be assessed at every study visit in this study. Liver chemistry will be monitored by measuring ALT, AST, alkaline phosphatase (ALP), GGT, total and direct bilirubin, total bile acids, prothrombin time (PT)/international normalized ratio (INR), and partial thromboplastin time (PTT). Testicular function will be monitored by measuring LH, FSH, inhibin B, and SHBG and performing scrotal ultrasounds. Thyroid function will be monitored via a thyroid panel that measures T3, T4, and TSH. Finally, strict individual treatment-stopping criteria for liver chemistry findings and criteria for increased liver chemistry monitoring are in place (see [Section 7.1.1](#) and [Section 13.2](#)).

The reversible histopathological effects of tildacerfont on the male reproductive tract in rat and dog toxicity studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a CRF₁ receptor antagonist, tildacerfont is intended to reduce abnormally elevated ACTH and androgen levels. In healthy animal models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, effects on male reproductive tissues may be expected as a

result of androgen reduction outside of the normal range. However, in patients with CAH, whose baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

The Sponsor believes that the benefit-to-risk profile of this study is favorable. Given the serious nature of CAH and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with CAH. Given 1) the acceptable overall safety and tolerability profile of tildacerfont in healthy volunteers and subjects with CAH; 2) the ability to monitor the observed risk of LFT elevation, which is reversible and occurred at higher exposures than those expected in this study; and 3) the evidence of reductions in ACTH, 17-OHP, and A4 at multiple dose levels tested in previous Phase 2 studies, the Sponsor believes that the benefit-to-risk profile favors the continued clinical investigation of tildacerfont, including this randomized, double-blind, placebo-controlled investigation of extended treatment with tildacerfont for up to 70 weeks in subjects with CAH. An optional Open-Label Extension Period will provide additional open-label treatment with tildacerfont at 200 mg QD for up to 240 weeks.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Efficacy	
Primary Efficacy	
To evaluate the effect of tildacerfont in reducing A4 in subjects with classic CAH over 12 weeks	Assessment of dose response for change from baseline in log A4 after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
Secondary Efficacy	
To evaluate the effect of tildacerfont in reducing A4 in subjects with classic CAH over 12 weeks	Change from baseline in A4 as assessed on the log scale after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing A4 in subjects with classic CAH over 12 weeks	Absolute change from baseline in A4 as determined via application of the delta theorem to the log scale analysis results after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing 17-OHP in subjects with classic CAH over 12 weeks	Assessment of dose response for change from baseline in log 17-OHP after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing 17-OHP in subjects with classic CAH over 12 weeks	Change from baseline in 17-OHP as assessed on the log scale after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing 17-OHP in subjects with classic CAH over 12 weeks	Absolute change from baseline in 17-OHP as determined via application of the delta theorem to the log scale analysis results after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
Exploratory Efficacy	
To evaluate the effect of tildacerfont in reducing A4 in subjects with classic CAH over 12 weeks	Proportion of subjects who achieve adequate control of A4 ($A4 \leq 1x, 1.25x, 1.5x, 1.75x$ and $2x$ ULN) after 12 weeks on

Objectives	Endpoints
	double-blind, placebo-controlled treatment (Week 18) for each treatment group
To evaluate the effect of tildacerfont in reducing 17-OHP in subjects with classic CAH over 12 weeks	Proportion of subjects who achieve adequate control of 17-OHP (17-OHP \leq 1200 ng/dL) after 12 weeks on double-blind, placebo-controlled treatment (Week 18) for each treatment group
To evaluate the effect of tildacerfont in reducing testicular adrenal rest tumor(s) (TART[s]) in male classic CAH subjects with TART(s) at baseline after 12 weeks on treatment	Change in the lesion volume of TART(s) from baseline after 12 weeks on double-blind, placebo-controlled treatment (Week 18) for each treatment group
To characterize dose-exposure of Tildacerfont in CAH	Correlation of Tildacerfont plasma concentration vs dose
To evaluate the effect of tildacerfont on biomarkers relative to each other in subjects with classic CAH over 12 weeks	Estimate the within subject correlation of A4 and 17-OHP log scale values over time
To evaluate the effect of tildacerfont in improving quality of life (QoL) in subjects with classic CAH after 12 weeks on treatment	Change from baseline in SF-36 total score after 12 weeks on double-blind, placebo-controlled treatment (Week 18) for each treatment group
To evaluate the effect of tildacerfont in improving QoL in subjects with classic CAH	Change from baseline at Week 76 in SF-36 total score across all ITT subjects
To evaluate the effect of tildacerfont in improving acne in classic CAH subjects with acne at baseline	Change from baseline at Week 76 in IGA of acne severity score across all ITT subjects with acne at baseline
To evaluate the effect of tildacerfont in improving hirsutism in female classic CAH subjects with hirsutism at baseline	Change from baseline at Week 76 in modified Ferriman Gallwey (mFG) score for hirsutism across all female ITT subjects with hirsutism at baseline
To evaluate the proportion of subjects who can reduce GC use in subjects with classic CAH	Proportion of subjects with at least a 5 mg/day hydrocortisone equivalent (HCe) reduction from baseline in GC dose and A4 \leq ULN at Week 76
To evaluate the effect of tildacerfont in reducing TART(s) in male classic CAH subjects with TART(s) at baseline	Change in the total lesion volume of TART(s) from baseline at Week 76 across all male ITT subjects with TART(s) at baseline
To evaluate the effect of tildacerfont in reducing A4 in subjects with classic CAH over 12 weeks	Assessment of dose response for change from baseline in log ATCH after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing ATCH in subjects with classic CAH over 12 weeks	Absolute change from baseline in ACTH as determined via application of the delta theorem to the log scale analysis results after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To evaluate the effect of tildacerfont in reducing ACTH in subjects with classic CAH over 12 weeks	Change from baseline in ACTH as assessed on the log scale after 12 weeks on double-blind, placebo-controlled treatment (Week 18)
To characterize dose-exposure of Tildacerfont in CAH	Estimate the within subject correlation of A4 and 17-OHP log scale values with tildacerfont plasma concentrations over time
<i>Exploratory Efficacy (Optional Open-Label Extension Period)</i>	
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels in subjects with CAH	Proportion of subjects with GC dose \leq 25 mg/day in HCe and A4 \leq ULN at end of treatment (EOT)

Objectives	Endpoints
To evaluate the percentage change in GC use in subjects with CAH	Percent change from baseline in GC dose at EOT
To evaluate the effect of tildacerfont in reducing cardiovascular risk in subjects with CAH and at least one cardiovascular risk factor at baseline	Proportion of subjects with improvement in at least one cardiovascular risk factor at EOT
To evaluate the effect of tildacerfont in reducing TART(s) in male CAH subjects with TART(s) at baseline	Proportion of male subjects with reduction in TART(s) at EOT who had TART(s) at baseline
Safety	
To evaluate the safety of tildacerfont in subjects with CAH	AEs, SAEs

4 STUDY DESIGN

4.1 Overall Design

This is a study with a 3-part treatment period that will evaluate the efficacy and safety of up to 70 weeks of treatment with tildacerfont in subjects with classic CAH who have elevated biomarkers at baseline. An optional Open-Label Extension Period will provide additional open-label treatment with tildacerfont at 200 mg QD for up to 240 weeks.

4.1.1 Study Periods

Refer to the study schematic provided in [Section 1.2](#).

This study will consist of the following periods:

- A \leq 45-day *Screening Period* for confirmation of eligibility
 - Optional A4 Screening Visit
 - Screening information captured within 45 days of Day 1 in this study (particularly screening information transferred from Spruce Biosciences Study SPR001-204 to this study) may be used to determine eligibility and fulfill screening requirements for this study.
- A 6-week, single-blind, placebo *Run-in Period*, during which subjects will be assessed for adherence to their existing GC therapy and daily ingestion of placebo with food
- Subjects who continue to meet all eligibility criteria at the end of the Run-in Period will then enter a 3-part *Treatment Period*:
 - **Part A:** The first 12 weeks of the Treatment Period will be a randomized, double-blind, placebo-controlled, dose-ranging study. Subjects will be randomized in a 1:1:1:1 ratio to receive either placebo or tildacerfont at a dose of 50 mg QD, 100 mg QD, or 200 mg QD.

- **Part B:** During the second 12 weeks of the Treatment Period, all subjects will receive active drug (tildacerfont), with possible dose escalation for eligible subjects. Subjects and Investigators will remain blinded to previous treatment in Part A and dose level of tildacerfont in Part B.
 - Subjects who were randomized to placebo in Part A will receive tildacerfont at 100 mg QD at the beginning of Part B.
 - Subjects who were randomized to tildacerfont at 200 mg QD in Part A will continue to receive tildacerfont at 200 mg QD in Part B.
 - Subjects who were randomized to tildacerfont at 50 mg QD or 100 mg QD in Part A will continue to receive the same dose at the beginning of Part B if they have A4 ≤ULN at Week 18. These subjects will be escalated to the next highest dose at the beginning of Part B if they have A4 >ULN at Week 18 (ie, subjects previously on 50 mg QD would be escalated to 100 mg QD, and subjects previously on 100 mg QD would be escalated to 200 mg QD).

Based on the results of the Week 24 visit of Part B, subjects will have another opportunity for tildacerfont dose escalation if they have A4 >ULN and are tolerating their current dose of tildacerfont. Specifically:

- Subjects currently taking 50 mg QD will be escalated to 100 mg QD.
- Subjects currently taking 100 mg QD will be escalated to 200 mg QD.
- **Part C:** During the last 46 weeks of the Treatment Period, all subjects will be escalated to 200 mg QD, with periodic opportunities for GC adjustment for eligible subjects. Subjects and Investigators will continue to remain blinded to previous treatment in Part A and dose level of tildacerfont in Parts B and C.
 - Subjects with A4 ≤ULN at Week 38 or Week 46 will begin to reduce their daily GC dose level by increments of approximately 5 mg/day HCe each time, down to a minimum of 15 mg/day HCe (see [Section 6.5.1.4](#)).
- For subject's continuing into the optional Open-Label Extension Period
 - The Open-Label Extension Period will provide subjects with up to 240 weeks of treatment with tildacerfont 200 mg QD.
 - Subjects will be eligible to adjust GC dose level at each visit (see [Section 6.5.1.4](#)).
- A 30-day *Follow-up Period at EOT*
 - Subjects who do not continue to the Open-Label Extension Period upon completion of Treatment Period Part C will enter a 30-day Follow-up Period.
 - Upon completion of the Open-Label Extension Period, subjects will enter a 30-day Follow-up Period.
 - At the end of study treatment, subjects will maintain the GC regimen and mineralocorticoid regimen (as applicable) established during Part C until the 30-day follow-up visit unless the Investigator determines that the subject's clinical status necessitates a dosing change. After completion of the study, GC therapy will be managed at the discretion of the subject's treating physician.

Changes in GC dosing are generally not permitted during this study except after certain visits in Part C, the optional Open-Label Extension Period, and in the case of stress dosing throughout the study. During times of clinically significant physical stress such as intercurrent illness with fever, surgical procedures, or

significant trauma, stress dosing with extra GC (in the form of HC) for prevention of adrenal crisis will be allowed according to “sick day guidelines” (see [Section 6.5.1.5](#)).

4.1.2 Study Visits and Telephone Contacts

4.1.2.1 Study Visit Schedule

- During the Screening Period:
 - Screening Visit at ≤45 days before Day 1
 - Optional A4 Screening Visit ≤45 days before Day 1
- During the Run-in Period: visits at Day 1 and Week 4; scheduled telephone contact at Week 2
- During the Treatment Period:
 - Part A: visits every 4 weeks, at Week 6 (baseline) and at Weeks 10, 14, and 18; scheduled telephone contact at Week 8
 - Part B: visits every 6 weeks, at Weeks 24 and 30; scheduled telephone contact at Week 21
 - Part C: visits every 6 to 12 weeks, at Weeks 38, 46, and 58, 70, and 76; scheduled telephone contact at Week 52
- During the optional Open-Label Extension Period: Visits every 3 to 6 months at Weeks 88, 100, 124, 148, 172, 196, 220, 244, 268, 292 and 316
- At 30 days after the last dose of study drug for final safety follow-up
- PRN telephone contacts are detailed in [Section 4.1.2.3](#).

4.1.2.2 Mode of Study Visits in the Context of COVID-19 or Other Logistical Challenges

All efforts should be made to conduct visits in the clinic. Since the COVID-19 pandemic is expected to continue during the conduct of this trial, study visits can be adapted into a combination of in-clinic and telemedicine activities, with optional at-home visits, to mitigate the risk of COVID-19 infection associated with study participation and to accommodate local and individual circumstances while maintaining participant access to healthcare resources.

Some of the clinic activities of the Screening Visit may be conducted remotely (at the subject’s home) if approved by the site’s IRB/EC.

The EDC system will capture the mode by which data are collected for each visit/activity.

If home visits are conducted, the qualified medical professionals who will perform the study’s home visits are defined as individuals who meet national/local licensing requirements needed to perform the procedures required at the home visits. Their national/local licensure will be verified, and they will complete training on the study protocol and GCP. If the medical professional does not meet the national/local licensing requirements needed to perform the optional home visit activities (physical examination, acne IGA score, and hirsutism mFG score for females), the Investigator or Investigator-delegated study personnel must complete these activities for each visit.

Refer to [Section 11](#) for more information on study conduct in the context of COVID-19 or other logistical challenges.

4.1.2.3 Telephone Contacts

Sites will make scheduled telephone contacts to all subjects at Weeks 2, 8, 21, and 52 to record any AEs and concomitant medications. During the Week 2 telephone contact, sites will also confirm subject adherence to study activities.

After receiving A4 results, sites will make telephone contacts to applicable subjects concerning tildacerfont or GC adjustment.

- For subjects who are eligible for GC adjustment following the Week 38 and/or 46 study visits or during the optional Open-Label Extension Period, sites will contact these subjects by telephone within 2 weeks after the applicable study visit. The site will direct a subject to reduce his/her GC dose at that time if the subject has not experienced any change in clinical status since the previous study visit. If no GC dose adjustment is warranted based on the A4 level, the site does not need to contact the subject. If a subject's GC dose is adjusted, the site will telephone the subject again 7 days after the dose adjustment to assess for the occurrence of AEs and the initiation of new concomitant medications.

Subjects should be instructed to telephone sites if they have any concerns about their health.

PRN telephone contacts initiated by sites and telephone contacts initiated by subjects should be captured in the EDC system as "unscheduled" telephone contacts.

4.1.3 Study Diary/Drug Adherence Data Collection

Subjects will be asked to maintain an electronic study diary to capture daily information during the Run-in and Treatment Periods. The Investigator is responsible for ensuring that subjects record the appropriate information in their diaries. Subjects will document study drug and background GC adherence through Week 18. Female subjects will also use the study diary to record menstrual information (including start and stop dates of menses) across the full treatment period up to Week 76.

4.2 Scientific Rationale for Study Design

In previous Phase 2 studies, tildacerfont exhibited an acceptable safety profile and proof-of-concept efficacy in reducing ACTH, 17-OHP, and A4 levels in adult subjects with classic CAH, which support the continued clinical development of tildacerfont.

Previous Phase 2 studies of tildacerfont were open-label, smaller in sample size, and shorter in duration. The initial Phase 2 Study SPR001-201 was a dose-ranging study that treated 26 CAH subjects with tildacerfont for 2 weeks at each dose level ranging from 200 mg to 1000 mg per day. Efficacy was observed at all dose levels/regimens of tildacerfont tested without evidence of a dose trend in efficacy response. Thus, a clear exposure-response profile and an optimal dose were not established. The subsequent Phase 2 Study SPR001-202 enrolled 11 subjects with CAH (9 subjects who previously participated in Study SPR001-201 and 2 tildacerfont-naïve subjects) and treated them with tildacerfont 400 mg QD for 12 weeks. The magnitude of the efficacy response strengthened over 12 weeks of therapy, suggesting that the full treatment effect of tildacerfont may only be revealed after longer-term therapy and that the 2 weeks of treatment at each dose level in Study SPR001-201 may not have been long enough to effectively dose-range.

Study SPR001-203 will provide a placebo-controlled, powered, longer-duration, and more definitive dataset than previous Phase 2 studies. Study SPR001-203 will enroll approximately 72 subjects for a cumulative treatment duration of 70 weeks. The Treatment Period will consist of a 12-week, randomized, double-blind, placebo-controlled, dose-finding treatment period (Part A); followed by a 12-week treatment period in which all subjects are treated with active drug, with possible dose escalation (Part B); followed by a 46-week treatment period in which all subjects are treated with active drug, with possible GC adjustment (Part C). The placebo treatment group in Part A will control for any potential placebo effects in CAH patients and their impact on the overall tildacerfont treatment effect. Parts B and C will allow further monitoring for clinical outcomes associated with biomarker control, provide subjects randomized to placebo in Part A with active study drug, and in Part B, dose-escalate subjects who did not achieve response based on A4 \leq ULN. This dose-escalation strategy may help to determine whether a higher dose may be necessary for hormone control in subjects with higher baseline hormone levels. Study SPR001-203 will explore total daily doses of tildacerfont tablet \leq 200 mg with the objective of establishing a clear exposure-response profile and identifying an optimal dose for the management of CAH (see [Section 4.3](#) for justification of dose).

Eligibility for Studies SPR001-201 and SPR001-202 was based primarily on elevated 17-OHP. This contributed to the recruitment of a heterogeneous population of CAH patients that may have obscured the efficacy signal across different dose cohorts. Subgroup analyses of data from these studies using baseline A4 and ACTH levels to stratify subjects revealed 2 distinct subgroups of subjects that differed by their mean background GC dose at study entry and tildacerfont PD response profiles. These 2 subgroups had potentially different treatment goals. The subgroup of subjects with elevated A4 and ACTH showed greater, more consistent reductions in key hormones in response to tildacerfont treatment than the subgroup of subjects with lower A4 and ACTH. Subjects with elevated A4 and ACTH would require reductions in key hormones before any GC dose reduction and constitute an appropriate subpopulation of CAH patients for the current study design. Parts A, B, and C will provide this subject population with time to achieve hormone control on tildacerfont, with possible tildacerfont dose escalation in Part B to find the best dose for each subject. Additionally, Part C will provide those subjects who are able to achieve A4 control on tildacerfont with opportunities to reduce their GC dose. Study SPR001-203 has inclusion criteria based on elevated A4 to yield a more homogeneous study population from which to draw more robust conclusions.

Patients on dexamethasone are excluded from this study because dexamethasone may have a moderate drug interaction with tildacerfont that would confound efficacy analysis. GC exposure data from Study SPR001-201 showed a positive signal for drug-drug interaction (DDI) potential between tildacerfont and dexamethasone, with tildacerfont increasing dexamethasone exposures approximately 1.8-fold and with the lower bound of the associated 95% confidence intervals (CIs) generally above 1.0. See [Section 6.5.1.3](#) for more information.

An important goal of treatment in CAH is the reduction of adrenal hormone levels. To that end, this study will evaluate the effect of tildacerfont on A4 levels as its primary endpoint and the effect of tildacerfont on 17-OHP as a secondary endpoint. Exploratory efficacy endpoints will assess additional clinical benefit associated with biomarker control in terms of improvements to QoL, acne, hirsutism in females, and TARTs in males.

Another important goal of treatment in CAH is the reduction of GC dose requirements ([Speiser 2018](#)). To that end, Part C of this study and the optional Open-Label Extension Period will explore the potential GC-sparing effects of tildacerfont in subjects with elevated baseline A4 who are able to achieve A4 control on tildacerfont. In Part C, and in the optional Open-Label Extension Period, eligible subjects may begin to reduce their GC doses. The change from baseline in GC dose and the proportion of subjects with at least a 5 mg/day HCe reduction from baseline in GC dose at the end of Part C (while maintaining A4 \leq ULN) will be evaluated as an exploratory efficacy endpoint.

The placebo Run-in Period provides subjects time to acclimate to participation in a clinical study, which can often change subject behavior, before active therapy with tildacerfont is initiated. In the case of CAH patients participating in this study, behavior changes may include improved dosing adherence to background GC medications and alterations in daily routine (such as changes to sleep schedules and mealtimes) to accommodate morning laboratory assessments and daily study drug dosing with an evening meal. Such changes may produce effects on biomarkers independent of tildacerfont. The Run-in Period thus serves to ensure that subjects are on a stable baseline regimen of GC replacement therapy before the start of tildacerfont dosing and provides for more accurate and stable baseline data.

The 70-week treatment duration and the optional Open-Label Extension Period will provide longer-duration information than previous Phase 2 clinical studies on the effects of tildacerfont on adrenal hormones and on whether effects on other clinical outcome measures of concern can be achieved with tildacerfont. The 30-day post-treatment washout period allows for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

The schedule of study visits interspersed with telephone contacts provides an appropriate balance between minimizing subject burden and closely monitoring subjects for safety and response to therapy.

Study drug will be taken with a meal because Phase 1 clinical studies showed that taking tildacerfont in a fed state improves drug absorption. The meal should contain approximately 25 -50% fat content because high fat intake with study drug may increase drug accumulation.

Individual treatment-stopping criteria and appropriate laboratory and medical assessments have been established to ensure subject safety.

4.3 Justification for Dose

In Study SPR001-203, tildacerfont tablets will be administered at doses ranging from 50 mg to 200 mg QD with the objective of establishing a clear exposure-response profile and identifying an optimal dose for the management of CAH. Data from previous Phase 1 and Phase 2 studies support the safety and potential PD effects of these doses and provide the rationale for using these doses to achieve the aforementioned objectives.

The safety data show that tildacerfont has been generally well tolerated in all clinical studies to date, with no related SAEs. Specifically, tildacerfont at a dose of \leq 200 mg/day has been well tolerated in previous clinical studies.

The clinical efficacy/PD data show CRF₁ receptor target engagement (reductions in ACTH) and reductions in key adrenal hormones (17-OHP and A4) in subjects with CAH dosed for 2 weeks with 200 mg/day

tildacerfont, the lowest dose previously tested in subjects with CAH (see [Section 2.3.2](#)). However, efficacy was also observed at multiple dose levels/regimens of tildacerfont tested, without evidence of a dose trend in efficacy response. Thus, a clear exposure-response profile and an optimal dose have not been established.

A 1-compartment PK model with first-order absorption and elimination was fit to PK data from Study SPR001-201. This model was then used to estimate the steady-state exposure for each subject at each dose. For each of the 3 key hormones of ACTH, 17-OHP, and A4, an apparent plateau in response is observed at exposures achieved with the 200 mg/day dose of tildacerfont, with no additional benefit at the higher doses. This suggests the need for further dose-ranging at doses \leq 200 mg/day.

The long half-life of tildacerfont, estimated to be approximately 60 hours after single-dose administration, supports QD dosing in this study.

Guided by the safety, efficacy, and exposure-response analyses from available clinical data, Spruce has selected tildacerfont tablet doses of 50 mg, 100 mg, and 200 mg QD for testing in Study SPR001-203. These doses lie within a clinically precedented dose range that has been well tolerated and will help to establish a clearer exposure-response profile and an optimal dose.

4.4 End of Study

4.4.1 End of Study Definition

A subject is considered to have completed study treatment if the subject has completed all visits through Week 76 of the Treatment Period. A subject is considered to have completed the study if the subject has completed all phases of the study, including the final follow-up visit. The end of the study is defined as the date of the last follow-up visit of the last subject in the study.

4.4.2 Optional Open-Label Extension Period

Subjects who successfully complete all visits in the Treatment Period will be eligible to participate in an optional Open-Label Extension Period for up to 240 weeks of additional study treatment. If additional studies are warranted in the clinical development program for adult CAH or other unforeseen circumstances arise, the Open-Label Extension Period may be closed to further enrollment or discontinued early.

The end of the study is defined as the date of the last follow-up visit of the last subject in the study.

5 STUDY POPULATION

This study will randomize approximately 72 subjects with classic CAH currently receiving GC therapy into the start of the Treatment Period. The study will enroll subjects at approximately 130 investigative sites globally.

All applicable screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all individuals screened and to confirm eligibility or record reasons for screening failure, as applicable.

Screening information from the parallel Spruce Biosciences Study SPR001-204 may be used to determine eligibility and fulfill screening requirements for this study if the information was captured within 45 days before Day 1 in this study.

5.1 Eligibility Criteria

5.1.1 Inclusion Criteria

A subject must meet all of the following criteria to be eligible for this study:

1. Male and female subjects ≥ 18 years old at screening
2. Has a known childhood diagnosis of classic CAH due to 21-hydroxylase deficiency based on genetic mutation in *CYP21A2* and/or documented (at any time) elevated 17-OHP and currently treated with HC, HC acetate, prednisone, prednisolone, methylprednisolone (or a combination of the aforementioned GCs)
3. Has been on a stable, supraphysiologic dose of GC replacement (defined as ≥ 15 mg/day and ≤ 60 mg/day in HCe) for ≥ 1 month before screening
4. Has A4 $>$ ULN at both screening and Week 4 (measured before any AM GC dose) if daily GC dose < 30 mg OR has A4 $> 2.5 \times$ ULN at both screening and Week 4 (measured before any AM GC dose)
5. For subjects with the salt-wasting form of CAH, subject has been on a stable dose of mineralocorticoid replacement for ≥ 1 month before screening
6. Agrees to follow contraception guidelines ([Section 5.2.5](#)). Male subjects must also agree to refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug.
7. Is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol.

5.1.2 Exclusion Criteria

A subject will not be eligible for this study if he/she meets any of the following criteria:

1. Has a known or suspected diagnosis of any other known form of classic CAH (not due to 21-hydroxylase deficiency)

2. Has a history that includes bilateral adrenalectomy or hypopituitarism
3. Has a history of allergy or hypersensitivity to tildacerfont, any of its excipients, or any other CRF₁ receptor antagonist
4. Current treatment with dexamethasone as GC therapy for CAH
 - a. Prior treatment with dexamethasone is allowed as long as the transition to an alternative GC regimen (eg, HC, prednisone, or prednisolone) has resulted in a stable dose of GC replacement for ≥ 1 month before screening.
5. Is not adherent to GC or study drug dosing regimen during the Run-in Period (defined as taking <80% of expected doses based on drug accountability)
6. Shows clinical signs or symptoms of adrenal insufficiency
7. Has had a clinically significant unstable medical condition, medically significant illness, or chronic disease occurring within 30 days of screening, including but not limited to:
 - a. An ongoing malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
 - b. eGFR of <45 mL/min/1.73 m²
 - c. Current or history of liver disease (with the exception of Gilbert's syndrome).
 - d. History of alcohol or substance abuse within the last year, or any significant history of alcohol or substance abuse that would likely prevent the subject from reliably participating in the study, based on the opinion of the Investigator
 - e. Active hepatitis B, hepatitis C, or HIV at screening
 - f. Subjects who plan to undergo bariatric surgery during the study are excluded.
 - g. Any other condition that would impact subject safety or confound interpretation of study results
8. Psychiatric conditions, including but not limited to bipolar disorder, schizophrenia, or schizoaffective disorders that are not effectively controlled on medication and may have an adverse impact on study compliance. Symptoms including hallucinations, delusions, and psychosis are exclusionary.
Additionally:
 - a. Increased risk of suicide based on the Investigator's judgment or the results of the C-SSRS conducted at screening and Week 6 (eg, C-SSRS Type 3, 4, or 5 ideation within the past 6 months or any suicidal behavior within the past 12 months)
 - b. HADS score >12 for either depression or anxiety at screening or Week 6
9. Has clinically significant abnormal ECG or clinical laboratory results. Abnormal results that must be reviewed and discussed with the Medical Monitor to determine eligibility for this study include but are not limited to:
 - a. Any clinically meaningful abnormal ECG results, including QTcF >450 ms for male participants or >470 ms for female participants
 - b. ALT >2x ULN
 - c. Total bilirubin >1.5x ULN
 - d. Total bile acids >5x ULN

10. Routinely works overnight shifts
11. Subjects with travel plans/work schedules that result in significant and frequent changes in time zones (>2 hours) will require Medical Monitor approval for enrollment.
12. Females who are pregnant or nursing
13. Use of any other investigational drug from 30 days or 5 half-lives (whichever is longer) before screening to the end of the study
14. Use of the following drugs from 30 days or 5 half-lives (whichever is longer) before Day 1 to the end of the study:
 - a. Rosiglitazone, aromatase inhibitors, testosterone, growth hormones, or any other medication or supplement that could impact subject safety or confound interpretation of study results
 - b. The drugs listed in [Section 13.1](#), which are:
 - i. Moderate to strong inhibitors and/or inducers of CYP3A4
 - ii. Sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 (except hormonal contraception containing ≤ 35 μ g ethinyl estradiol)
 - iii. Sensitive substrates or narrow-therapeutic-range substrates of BCRP (except those that can be administered QD in the morning, separated by approximately 10 hours from evening administration of study drug)
15. Donation or receipt of blood from 90 days before Screening to the end of the study; donation or receipt of platelets, white blood cells, or plasma from 30 days before Screening to the end of the study

5.2 Lifestyle Considerations

5.2.1 Shift Work and Time Zone Changes

Given the circadian rhythm of HPA-axis hormones, the dosing of study drug with an evening meal, and early morning blood draws for laboratory assessments, subjects who routinely work overnight shifts are not eligible for this study, and subjects with travel plans/work schedules that result in significant and frequent changes in time zones (>2 hours) require Medical Monitor approval for enrollment.

5.2.2 Meals and Dietary Restrictions

Study drug must be consumed with food. Study drug will be consumed between 6 PM and midnight, with an evening meal. The evening meal should contain approximately 25-50% fat content. Study drug may be consumed up to 30 minutes after completing the evening meal, if necessary. If a subject has not consumed study drug within 30 minutes after the evening meal, the subject should consume study drug with a snack. Guidance on appropriate food content will be provided separately.

Subjects will be advised to refrain from consumption of grapefruit, grapefruit juice, or any fruits that are known to be strong CYP3A4 inhibitors from 1 day before the first dose of study drug until after the final dose.

5.2.3 Caffeine, Alcohol, and Tobacco

Subjects will abstain from imbibing alcohol within 12 hours before the blood draw (after 8 PM).

Subjects should not use nicotine-containing products or drink caffeinated beverages within 30 minutes before any study-related procedure.

5.2.4 Activity

Subjects should abstain from strenuous exercise for 8 hours before each study visit. Strenuous exercise might cause temporary spikes in biomarkers that could confound analysis of the effect of study drug.

Subjects should not exercise within 30 minutes before any study-related procedure.

5.2.5 Contraception Guidelines

5.2.5.1 Contraception Guidelines for Male Subjects

A male enrolling in this study must meet ONE of the following contraceptive criteria from Screening until 90 days after the last dose of study drug:

1. Is sexually abstinent from penile-vaginal intercourse as his usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent from Screening until 90 days after the last dose of study drug
2. Is vasectomized and the absence of sperm has been confirmed
3. Agrees to use a male condom AND female partner uses/has in place one of the following highly effective contraceptive methods from Screening until 90 days after the last dose of study drug:
 - a. Combined hormonal contraception (containing estrogen and progestogen) associated with inhibition of ovulation: oral, intravaginal, or transdermal
 - b. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
 - c. Intrauterine device (IUD)
 - d. Intrauterine system (IUS)
 - e. Bilateral tubal occlusion

5.2.5.2 Contraception Guidelines for Female Subjects

A female enrolling in this study must meet ONE of the following contraceptive criteria from Screening until 30 days after the last dose of study drug:

1. Is postmenopausal at Screening

A postmenopausal state is defined as no menses for at least 1 year without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, a single FSH measurement is insufficient to establish a postmenopausal state without at least 1 year of amenorrhea.

2. Has documentation of one of the following performed before Screening:
 - a. Hysterectomy
 - b. Bilateral salpingectomy
 - c. Bilateral oophorectomy
3. Is sexually abstinent from penile-vaginal intercourse as her usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent from Screening until 30 days after the last dose of study drug
4. Any male sexual partner is vasectomized, and the absence of sperm has been confirmed
5. Agrees to use one of the following highly effective contraceptive methods, which must be in place from at least 1 month before Screening until 30 days after the last dose of study drug:
 - a. Combined hormonal contraception (containing estrogen and progestogen) associated with inhibition of ovulation: oral, intravaginal, or transdermal

Any hormonal contraception containing ethinyl estradiol must contain $\leq 35 \mu\text{g}$ ethinyl estradiol, is permitted only for subjects who would not be considered at high risk for thromboembolic or cardiovascular complications with estrogen use, and must be used simultaneously with a backup method of contraception. Acceptable backup methods of contraception include diaphragm with spermicide, cervical cap with spermicide, vaginal sponge with spermicide, and male or female condom with or without spermicide. Dosing of oral formulations of hormonal contraception containing ethinyl estradiol should be offset by approximately 10 hours from the evening dose of study drug. The Investigator may consult with the Medical Monitor regarding such individuals.
 - b. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
 - c. IUD
 - d. IUS
 - e. Bilateral tubal occlusion

5.3 Screen Failures

Screen failures are defined as participants who consent to participate but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

If a subject fails to meet eligibility criteria during or at the end of the Run-in Period, the investigational site will schedule an abbreviated early termination visit to review AEs and concomitant medications and perform an abbreviated physical examination (preferably in the clinic, but also permissible via home visit).

Individuals who do not meet the following criteria for participation in the study may be rescreened according to the following guidelines:

- Individuals who do not meet the screening A4 inclusion criteria may be rescreened if their GC replacement dose is reduced and stable for ≥ 1 month. The Investigator will first consult with the Medical Monitor regarding such individuals. Any morning dose of GC medication should be taken after the screening blood draw to allow for an unimpeded assessment of hormones.
- Individuals on incompatible or excluded concomitant medications may be rescreened after an appropriate washout period (eg, 30 days or 5 half-lives, whichever is longer). The Investigator will first consult with the Medical Monitor regarding such individuals.
- Individuals who have an exclusionary laboratory value during the screening period may be retested before the start of the Treatment Period if the Investigator believes that the prior laboratory value is not consistent with the individual's overall clinical picture. The Investigator will first consult with the Medical Monitor regarding such individuals.

If appropriate, screening information transferred from Spruce Biosciences Study SPR001-204 to this study may be used to determine eligibility and fulfill screening requirements for this study.

6 STUDY INTERVENTION

6.1 Study Intervention Administration

6.1.1 Study Intervention Description

Tildacerfont is a small-molecule CRF₁ receptor antagonist.

Details about the physical, chemical, and pharmaceutical properties of tildacerfont are provided in the IB.

Study drug is defined as either tildacerfont or placebo.

Study treatment is defined more broadly as study drug or HC for stress dosing provided by the Sponsor.

6.1.2 Treatment Assignment, Dosing, and Administration

Subjects will use their own physician-prescribed supply of GCs as prescribed during the study, including during the Run-in Period.

Subjects will take placebo (during the Run-in Period) or assigned study drug (during the Treatment Period) orally each day between 6 PM and midnight, with an evening meal. The evening meal should contain approximately 25-50% fat content. Study drug may be consumed up to 30 minutes after completing the evening meal, if necessary.

During Part A (the first 12 weeks of the Treatment Period), subjects will be randomized in a 1:1:1:1 ratio to receive either placebo or tildacerfont at a dose of 50 mg QD, 100 mg QD, or 200 mg QD.

During Part B (the second 12 weeks of the Treatment Period) and Part C (the last 46 weeks of the Treatment Period), all subjects will receive active drug (tildacerfont).

- Subjects who were randomized to placebo in Part A will receive tildacerfont 100 mg QD at the beginning of Part B.
- Subjects who were randomized to tildacerfont 200 mg QD in Part A will continue to receive tildacerfont at 200 mg QD throughout Parts B and C.
- Based on A4 results from the Weeks 18 and 24 study visits, eligible subjects may undergo a tildacerfont dose escalation after each of these study visits. Specifically:
 - Subjects taking tildacerfont 50 mg QD will either continue to receive the same dose (if A4 ≤ULN) or be escalated to tildacerfont 100 mg QD (if A4 >ULN and the subject is tolerating his/her current tildacerfont dose)
 - Subjects taking tildacerfont 100 mg QD will either continue to receive the same dose (if A4 ≤ULN) or be escalated to tildacerfont 200 mg QD (if A4 >ULN and the subject is tolerating his/her current tildacerfont dose).
- At Week 30, all subjects will be escalated to 200 mg QD.

Immediately following the Weeks 18 and 24 visits, subjects will continue to take their previously assigned study drug until A4 laboratory results are received, the RTSM system determines the appropriate tildacerfont doses for the next portion of the study, and subjects receive their tildacerfont doses for the next portion of the study. Subjects will receive enough previously assigned study drug to last until they receive their appropriate tildacerfont dose for the next portion of the study. Subjects will either return to the clinic to pick up their study drug or will be shipped their study drug.

During the optional Open-Label Extension Period, subjects will continue to receive tildacerfont at 200 mg QD.

Only authorized study staff may dispense study drug. Sites will provide subjects with dosing instructions. The Sponsor will provide GC for periods of stress dosing. Sponsor-provided HC for stress dosing may be shipped directly to subjects.

Instructions for concomitant GC medication dosing are provided in [Section 6.5.1](#). Criteria for study drug discontinuation are provided in [Section 7.1](#).

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

The Investigator is responsible for study treatment receipt and accountability, reconciliation, and record maintenance.

6.2.2 Formulation, Appearance, Packaging, and Labeling

The drug product is formulated as a tablet containing 50 mg and/or 200 mg of drug substance and the following inactive ingredients: lactose monohydrate, hydroxypropyl cellulose, sodium lauryl sulfate,

microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and Opadry® yellow.

Placebo will be supplied as tablets that look identical to drug product but contain no drug substance.

Study drug tablets will be supplied in blister cards. [For the optional Open-Label Extension Period, study drug will be supplied either in blister card or in bottle pack.](#)

HC tablets for stress dosing will be supplied by the Sponsor in bottles.

6.2.3 Product Storage and Stability

All study treatment should be stored at room temperature, protected from light. Study treatment must be stored in a secure, environmentally controlled area that is monitored (manually or automatically) and accessible only to the Investigator and authorized study staff. Further details on the acceptable storage range for each study treatment are available in the study pharmacy manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

All subjects will receive single-blinded placebo during the Run-in Period.

All subjects will be centrally randomized to study intervention in Part A and assigned to the appropriate dose of tildacerfont in Parts B and C using an RTSM system. Subjects will be randomized using the following strata: A4 \leq 4x ULN and A4 $>$ 4x ULN.

Investigators, subjects, and the Sponsor's contract research organization (CRO) will be blinded to assigned study intervention in Part A and to dose of tildacerfont in Parts B and C. To maintain the blind, all subjects will receive the same number of study drug tablets per dose, with the appropriate number of tildacerfont and/or placebo tablets for the assigned study intervention. The primary efficacy analysis is planned after all subjects have completed Week 18, at the end of the double-blind treatment period. The subject level blind will be maintained until the completion of the primary efficacy analyses. The Sponsor and CRO's will be unblinded at the time of the primary efficacy analysis (Part A--- Week 18), but Investigators, , and subjects will remain blinded to each subject's treatment assignment during Part B.

Emergency unblinding to a subject's treatment assignment should only occur when knowledge of the treatment assignment is necessary for immediate medical management of the subject. If emergency unblinding is required, the Investigator may use the code provided at the site initiation visit to access the subject's treatment assignment details via the RTSM system.

6.4 Study Intervention Compliance

Subjects will be asked to document study drug and background GC adherence in their electronic study diaries through Week 18 (see [Section 4.1](#)). Subjects will return study drug at each study visit to conduct accountability. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol.

Each subject's compliance information will be reviewed during the Run-in Period to determine eligibility for entering the Treatment Period and then will be reviewed on an ongoing basis for subjects who enter

the Treatment Period. Compliance information to be reviewed will include (but not be limited to), adherence to the subject's background GC regimen, adherence to the study drug regimen (including taking as instructed with food), adequate recording of data in the study diary.

6.5 Concomitant Therapy

Concomitant medication is any medication (including over-the-counter [OTC] medication, prescription medication, vaccines, vitamins, and supplements) that the subject is receiving at screening or receives during the study. All concomitant medications must be recorded, along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

All concomitant medications should be compared against the list of prohibited medications and the list of other medications of concern provided in [Section 13.1](#). Subjects should be instructed to contact the site immediately any time a new medication is required during the course of the study, including prescription and OTC medications, even those to be used for only a short period of time (e.g., antibiotics, cold and flu remedies, GI therapies, opioids or other pain relievers). The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Glucocorticoid Replacement Therapy

6.5.1.1 General Procedures for Glucocorticoids

Information to be collected at screening about a subject's current and historical GC therapy for the past year include the type(s) of GC, the regimen(s), reason(s) that the subject is/was on that particular GC regimen, and any GC stress dosing during the past year.

To be eligible for this study, subjects must be on a stable dose of GC replacement ≥ 15 mg/day and ≤ 60 mg/day in HCe (see [Section 6.5.1.2](#) for GC dose conversion to HCe) for ≥ 1 month before screening without any evidence of non-adherence to the GC regimen during this period (stress dosing is allowed). Changes in GC dosing are generally not permitted during this study except during Part C and in the case of stress dosing throughout the study (see [Section 6.5.1.5](#)). If a change in a subject's long-term GC regimen is clinically indicated outside of Part C (eg, the subject experiences symptoms of chronic adrenal insufficiency), study drug will be discontinued. Subjects who discontinue study drug for this reason should complete the early termination follow-up visit.

Subjects with the salt-wasting form of CAH must also be on a stable dose of mineralocorticoid replacement for ≥ 1 month before screening. A change to a subject's GC regimen during Part C could necessitate an adjustment to the subject's mineralocorticoid regimen. The adequacy of a subject's mineralocorticoid dose should be monitored and adjusted as needed to adequately maintain standing blood pressure, plasma renin levels, and electrolytes (serum potassium in particular) within acceptable ranges ([Speiser 2018](#)).

On the evenings before scheduled laboratory assessments, subjects should take their evening GC dose before 10 PM. On the mornings of scheduled laboratory assessments, subjects should delay taking any morning dose of GC medication until after the laboratory assessments have been completed. On all

other days during the study, subjects should take their GC medication at the usual time(s). Mineralocorticoid may be taken at any time of day, but its timing relative to laboratory assessments should be consistent throughout the study.

6.5.1.2 Glucocorticoid Dose in Hydrocortisone Equivalents

[Table 1](#) defines the potencies of various GCs relative to HC in treating CAH. These conversion factors will be used to determine whether a subject's daily GC dose satisfies study eligibility criteria and provide general guidelines for GC adjustment in Part C.

Note that fludrocortisone (a mineralocorticoid, not a GC) should not be converted to HCe or included in the calculation of a subject's total daily GC dose.

Table 1. Relative Potencies of Glucocorticoids in Hydrocortisone Equivalents (HCe)

Glucocorticoid	Potency in CAH (HCe)
Hydrocortisone	1
Prednisone	4 ¹
Prednisolone or methylprednisolone	5 ^{1,2}

¹[Zoorab 1998](#). ²[Clayton 2002](#). The protocol uses a 1:4 ratio for HC: prednisone and 1:5 for HC:prednisolone. However, transitioning from prednisolone to prednisone will require the closest approximation possible given the denomination of tablets available. Switching from 1mg prednisolone to 1mg prednisone is the closest approximation possible and therefore is not a protocol deviation.

6.5.1.3 Exclusion of Concomitant Dexamethasone

Subjects cannot be on dexamethasone during the study. Based on nonclinical and Phase 1 clinical data, tildacerfont is a moderate inhibitor of CYP3A4. Dexamethasone is primarily metabolized through CYP3A4, and Phase 2 clinical data have shown a potential for DDI between tildacerfont and dexamethasone. Thus, use of dexamethasone as GC therapy for CAH is not permitted during this dose-finding study.

Prior treatment with dexamethasone is allowed as long as the transition to an alternative GC (eg, HC, prednisone, prednisolone) has resulted in a stable dose of GC replacement for ≥ 1 month before screening. Prednisone/prednisolone and HC are metabolized through multiple pathways, with CYP3A4 comprising <18% of its metabolism ([Kovacs 2019](#), [Ohno 2008](#)). Based on static mechanistic modeling used to predict drug-drug interactions ([FDA 2000](#)), no clinically relevant increase in GC exposure is expected with prednisone/prednisolone or HC and tildacerfont. Phase 2 clinical data have shown a low likelihood of a DDI with tildacerfont.

6.5.1.4 Guidance for Changing Glucocorticoid Regimens in Part C and Optional Open-Label Extension Period

In Treatment Period Part C, subjects with A4 \leq ULN at Week 38 or Week 46 will begin to reduce their daily GC dose level in increments of approximately 5 mg/day HCe each time, per [Table 1](#).

In the optional Open-Label Extension Period, subjects will be eligible to adjust GC dose level at each visit. Subjects with A4 \leq ULN at any lab assessment will begin to reduce their daily GC dose level in increments of approximately 5 mg/day HCe each time, per [Table 1](#).

Per Investigator judgment, adjustments may also be made to the morning/afternoon/evening distribution of a subject's GC regimen without changing the total daily GC dose. Adjustments of GC dose may proceed so long as the adjustment is not precluded by an untoward clinical sign or symptom.

Changes to dosing frequency, ie, TID to BID, should be discussed with the Medical Monitor.

- Subjects with an A4 measurement of \leq ULN at Week 38, Week 46, or during the Open-Label Extension Period will begin to reduce their daily GC dose. Each reduction of the daily GC dose will be by approximately 5 mg/day HCe, down to a minimum of 15 mg/day in HCe (approximately physiologic replacement level). Reduction may stop at a GC level >15 mg/day in HCe based on Investigator judgment.
- If a subject has an A4 measurement of >1.25 x ULN, the subject's daily GC level should be increased by approximately 5 mg/day HCe each time.
- The daily GC level will generally remain unchanged for subjects with A4 levels $>$ ULN and ≤ 1.25 x ULN, unless a change in the GC dose level is clinically indicated (per Investigator judgment and discussion with the Medical Monitor).
- If a subject experiences a clinically significant episode of adrenal insufficiency due to undertreatment (as opposed to an acute stressor), the subject's daily GC dose should be increased by approximately 5 mg/day HCe and should not be reduced again to the GC dose level associated with adrenal insufficiency (per Investigator judgment and discussion with the Medical Monitor).

Sites will contact subjects by telephone within 2 weeks after each applicable study visit regarding GC dose adjustments. Sites will telephone subjects again 7 days after each GC dose adjustment to assess for the occurrence of AEs and the initiation of new concomitant medications.

6.5.1.5 Stress Dosing of Glucocorticoid

During times of clinically significant physical stress such as intercurrent illness with fever, surgical procedures, or significant trauma, subjects may take extra GC (in the form of HC) consistent with the "sick day guidelines" for prevention of adrenal crisis shown in [Table 2 \(Bornstein 2016\)](#). Sites may employ variations on these guidelines, consulting with the Medical Monitor, if possible, in non-urgent situations. The Sponsor will provide all subjects with oral HC for the purposes of stress dosing ([Section 6.2.2](#)). For subjects who are not taking HC as their background GC regimen, the stress dose of HC should be estimated based on the relative potencies of GCs outlined in [Table 1](#).

The stress doses recommended in [Table 2](#) are meant to *replace* a subject's usual daily GC dose; they are NOT taken *in addition* to the subject's usual daily GC dose. When taking the stress dose orally, the subject should take the entire stress dose using HC tablets from the bottle provided by the Sponsor. The subject's physician-prescribed GCs should be temporarily held during stress dosing and reinstated as soon as the stress dosing period ends.

While all GC stress doses should be entered into the EDC, changes to usual daily GC dose only need to be entered into EDC when there is a definitive long-term, chronic alteration in the usual daily GC dosing regimen.

Table 2. Sick Day Guidelines for Stress Dosing of Hydrocortisone

Condition	Stress Dosing of Hydrocortisone
Home management of fever >38 °C (>100.4 °F) or illness requiring bed rest, when requiring antibiotics for an infection, or before undergoing a minor outpatient procedure (eg, dental work)	<ul style="list-style-type: none">Approximately double the routine oral GC dose (and give as HC) until recovery (usually 2 to 3 days)For fever >39 °C (102.2 °F) only, approximately triple the routine oral GC dose (and give as HC) until recovery (usually 2 to 3 days)¹Increase consumption of electrolyte-containing fluids and simple and complex carbohydrates (El-Maouche 2018), as tolerated
Unable to tolerate oral medication due to gastroenteritis or trauma	<ul style="list-style-type: none">HC 100 mg IM or SC
Minor to moderate surgical stress	<ul style="list-style-type: none">HC 25 to 75 mg/24 hours (usually 1 to 2 days)
Major surgery with general anesthesia, trauma, or disease that requires intensive care	<ul style="list-style-type: none">HC 100 mg IV injection, followed by HC 200 mg/24 hours (via continuous IV infusion or 50 mg bolus every 6 hours IV or IM)Weight-appropriate continuous IV fluids with 5% dextrose and 0.2% or 0.45% NaClRapid tapering and switch to oral regimen depending on clinical state
Acute adrenal crisis	<ul style="list-style-type: none">HC 100 mg IV injection, followed by HC 200 mg/24 hours (via continuous infusion or 50 mg every 6 hours IV or IM), reduced to HC 100 mg/day the following dayRapid infusion of 1000 mL isotonic saline within the first hour or 5% glucose in isotonic saline, followed by continuous IV isotonic saline guided by individual patient needsFor hypoglycemia: 0.5 to 1 g/kg dextrose or 2 to 4 mL/kg of D25W (maximum single dose 25 g) infused slowly at rate of 2 to 3 mL/minCardiac monitoring: rapid tapering and switch to oral regimen depending on clinical state

Abbreviations: D25W, dextrose 25% in water; GC, glucocorticoid; HC, hydrocortisone; IM, intramuscular; IV, intravenous; SC, subcutaneous.

¹When tripling the routine oral GC dose, the HC stress dose should be rounded up to the next highest 10-mg HC tablet.

To prevent hypoglycemia, the subject should drink small amounts of clear sugar-containing liquids frequently and/or consume carbohydrates if the subject is able, glucose monitoring should be considered, and IV sodium and glucose replacement may be required ([Clayton 2002](#); [Merke and Bornstein 2005](#); [Keil 2010](#)).

Day-to-day physical or psychological stressors, such as a short-term strenuous activity or school examinations, do not require increased GC dosing ([Clayton 2002](#); [Crown & Lightman 2005](#); [Merke and Bornstein 2005](#)).

Subjects will maintain stress dosing until symptoms subside (or according to the clinical judgment of the treating physician), then return to their usual GC regimen. Any scheduled lab draws should be delayed until 5 to 7 days after subjects first return to their usual GC regimen. Any study visit delayed because of stress dosing will not be considered a protocol deviation. Extra unscheduled study visits for safety follow-up may be conducted in the interim.

6.5.1.6 Post-Treatment Glucocorticoid Dosing

Upon completion of the Treatment Period, subjects will maintain the GC regimen and mineralocorticoid regimen (as applicable) established during Part C until the 30-day follow-up visit unless the Investigator determines that the subject's clinical status necessitates a dosing change. After completion of the study, GC therapy will be managed at the discretion of the subject's treating physician.

6.5.2 Prohibited Concomitant Medications

Other investigational drugs are prohibited during the study.

Rosiglitazone is prohibited during the study because it could affect the subject's ACTH levels. Aromatase inhibitors, testosterone, and growth hormones are also prohibited because these medications could affect the subject's total androgen levels. In general, subjects who require ongoing treatment with these medications should not be screened.

Any other medication or supplement that could impact subject safety or confound interpretation of study results is prohibited during the study.

6.5.2.1 Inducers or Inhibitors of CYP3A4

In vitro CYP reaction phenotyping has indicated that tildacerfont is metabolized by CYP3A4. Therefore, drugs that are known to be moderate to strong inducers or inhibitors of CYP3A4 are prohibited. Use of dexamethasone is not permitted during the study (see [Section 6.5.1.3](#)). Subjects will be advised to refrain from consumption of grapefruit, grapefruit juice, or any fruits that are known to be strong CYP3A4 inhibitors from 1 day before the first dose of study drug until after the final dose.

6.5.2.2 Substrates of CYP3A4 and/or BCRP

In vitro drug interaction studies coupled with physiologically based pharmacokinetic (PBPK) modeling have indicated that tildacerfont has the potential to inhibit CYP3A4 and BCRP. Tildacerfont has also demonstrated the potential to induce CYP3A4 (mRNA), but the net effect on CYP3A4 is moderate inhibition. Phase 1 clinical data have also confirmed that tildacerfont is a moderate inhibitor of CYP3A4. Therefore, drugs that are sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 and/or BCRP must be avoided. Sensitive substrates or narrow-therapeutic-range substrates of BCRP that are not also metabolized by CYP3A4 and that can be administered QD in the morning (separated by approximately 10 hours from evening administration of study drug) may be permitted with monitoring for safety.

Sensitive substrates are drugs whose plasma area under the concentration-time curve (AUC) has been shown to increase ≥ 5 -fold when co-administered with a known inhibitor of the enzyme and drugs for which the AUC in poor metabolizers is >5 -fold the AUC in extensive metabolizers. Drugs with narrow therapeutic ranges are those for which even small increases in a subject's exposure to these drugs (potentially induced by the concomitant use of tildacerfont) could lead to serious safety concerns (e.g., torsades de pointes).

Ethinyl estradiol is a CYP3A4 and BCRP substrate, and tildacerfont may increase the level of ethinyl estradiol by <1.25 -fold. With ethinyl estradiol doses ≤ 35 μ g, exposure to ethinyl estradiol is unlikely to reach the threshold associated with increased thromboembolic or cardiovascular risk that is observed with higher-dose ethinyl estradiol formulations. Thus, any hormonal contraception containing ethinyl estradiol used by female subjects must contain ≤ 35 μ g ethinyl estradiol, is permitted only for subjects who would not be considered at high risk for thromboembolic or cardiovascular complications with estrogen use, and must be used simultaneously with a backup method of contraception according to [Section 5.2.5.2](#). Dosing of oral formulations of hormonal contraception containing ethinyl estradiol should be offset by approximately 10 hours from the evening dose of study drug.

[Section 13.1](#) provides a non-exhaustive list of medications that are prohibited because of their potential for metabolic interactions with tildacerfont. This list shows many commonly used medications, including certain antibiotics, antifungal agents (itraconazole, ketoconazole), statins (lovastatin, simvastatin), anti-inflammatory agents (felodipine), migraine remedies (eletriptan), anxiolytics (buspirone, midazolam), and drugs for erectile dysfunction (avanafil, sildenafil, vardenafil). (Many oncology drugs and medications used to treat the hepatitis C virus and HIV are strong inhibitors of CYP3A4 but are not listed simply because individuals with active cancer, hepatitis C, and/or HIV are excluded from this study.) It is critical that each subject's concomitant medications are carefully compared to the list in [Section 13.1](#).

In all cases, if there is a question or concern about a specific medication being used by the subject, it is appropriate to review the usage with the Medical Monitor before enrolling the subject in the study and/or making a change in concomitant medications.

7 STUDY DRUG DISCONTINUATION AND PARTICIPANT WITHDRAWAL

7.1 Study Drug Discontinuation

Subjects may voluntarily discontinue study drug at any time. The Investigator and/or Sponsor may also discontinue a subject's study drug at any time. When feasible, Investigators should discuss any safety concerns with the Medical Monitor as soon as possible to determine whether a subject should continue or discontinue study drug. Study drug will be discontinued in subjects who experience individual treatment-stopping criteria described in this section. The Sponsor and Investigator will make efforts (when possible) to continue to collect data (according to the Schedule of Post-Screening Activities) on subjects who discontinue study drug.

If study drug is discontinued, the Investigator will report the discontinuation to the Medical Monitor, document the date and reason for study drug discontinuation on the appropriate electronic case report

form (eCRF), schedule an early termination visit for the subject (see the Schedule of Post-Screening Activities in [Section 1.3.3](#)), provide or arrange for appropriate follow-up, and document the course of the subject's condition.

7.1.1 Liver Chemistry Stopping Criteria

Liver chemistry stopping criteria defined in [Table 3](#) are designed to ensure subject safety and to evaluate liver event etiology. The Investigator should notify the Sponsor within 24 hours of awareness if any of the criteria defined in [Table 3](#) are met. Further suggested actions, follow-up assessments, and monitoring assessments are provided in [Section 13.2](#). A significant change in liver chemistry that requires increased monitoring but does not necessarily satisfy stopping criteria may still be considered an adverse event of special interest (AESI) (see [Section 8.3.8](#)).

Table 3. Stopping Criteria and Increased Monitoring for Liver Chemistry Elevations

Criteria	Actions	
ALT \geq 5x ULN	Discontinue study drug and notify Sponsor.	
ALT \geq 3x ULN	AND total bilirubin \geq 2x ULN (>35% direct bilirubin) ¹	Discontinue study drug and notify Sponsor. Possible Hy's Law case— report as SAE .
	AND INR >1.5	Discontinue study drug and notify Sponsor. Possible Hy's Law case— report as SAE .
	AND subject has symptoms (new or worsening) believed to be related to liver injury or hypersensitivity ²	Discontinue study drug and notify Sponsor.
	AND total bile acids >3x ULN	Withhold study drug and notify Sponsor. Repeat liver chemistry tests after 1 week, and discuss with Medical Monitor whether to discontinue study drug.
	ALT \geq 3x ULN only	Monitor weekly for 4 weeks while continuing study drug and notify Sponsor (see Section 13.2.2)
	AND cannot be monitored weekly for 4 weeks	Discontinue study drug and notify Sponsor.
	persists for \geq 4 weeks	Discontinue study drug and notify Sponsor.

Abbreviations: ALT, alanine aminotransferase; INR, international normalized ratio; SAE, serious adverse event; ULN, upper limit of normal.

¹ If serum bilirubin fractionation is not immediately available, discontinue study drug if ALT \geq 3x ULN and bilirubin \geq 2x ULN and record the presence/absence of detectable urinary bilirubin on dipstick, which is indicative of direct bilirubin elevations suggesting liver injury.

² Symptoms related to liver injury include fatigue, nausea, vomiting, right upper quadrant pain or tenderness, and jaundice. Symptoms related to hypersensitivity include fever, rash, and eosinophilia.

7.1.2 QT Stopping Criteria

Study drug will be discontinued for a subject if either of the following criteria is met:

- QTcF >500 msec OR uncorrected QT >600 msec
- Change from screening or baseline in QTcF of >60 msec

One repeat ECG should be performed to confirm the accuracy and persistence of an initial result that fulfills the QT stopping criteria.

7.1.3 Suicidality Stopping Criteria

Tildacerfont is considered to be a central nervous system (CNS)-active drug. Some CNS-active drugs may be associated with an increased risk of suicidal ideation in certain populations. Although tildacerfont has not been shown to be associated with an increased risk of suicidal thinking or behavior in past clinical studies, subjects will be monitored for such events during this study using the C-SSRS (see [Section 8.2.6.1](#)).

Individuals who answer “yes” to Question 3, 4, or 5 in the suicidal ideation section of the C-SSRS at screening or Week 6 are not eligible for this study. Any subject who exhibits any Suicidal Behavior or Suicidal Ideation (eg, answers “yes” to Question 3, 4, or 5 in the suicidal ideation section of the C-SSRS) will have study drug immediately discontinued and should be evaluated by a psychiatrist. This safety finding will be considered an AESI if it is not an SAE (eg, requiring hospitalization) (see [Section 8.3.8](#)).

7.1.4 Depression or Anxiety Stopping Criteria

Individuals who score >12 on either the depression or anxiety subscale of the HADS (see [Section 8.2.6.2](#)) at screening or Week 6 are not eligible for this study. Any subject who develops severe depression or anxiety (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or higher), as assessed by the Investigator, will require study drug discontinuation and appropriate follow-up. This will be considered an AESI if it is not an SAE (eg, requiring hospitalization) (see [Section 8.3.8](#)).

7.1.5 Adrenal Insufficiency Stopping Criteria

Symptoms of adrenal insufficiency include weakness, tiredness, anorexia, nausea, vomiting, abdominal pain, orthostasis and muscle and joint aches. Weight loss and hypotension (ie, systolic blood pressure <90 mmHg) are also associated with adrenal insufficiency. Hyponatremia, hyperkalemia, hypercalcemia, azotemia, anemia and eosinophilia may accompany adrenal insufficiency. It is important to note that many of these signs, symptoms and laboratory findings are nonspecific and commonly occur in persons without adrenal insufficiency. The Investigator should use their clinical judgment when determining whether the signs, symptoms or laboratory findings are isolated adverse events or are possibly due to adrenal insufficiency.

The Investigator is strongly encouraged to contact the Medical Monitor to review the presentation and discuss the plan for a subject with any potential AE of adrenal insufficiency.

If the Investigator deems the sign(s), symptom(s) and/or laboratory finding(s) to be due to adrenal insufficiency, the AE should be recorded as adrenal insufficiency. The sign(s), symptom(s) and laboratory

findings resulting in the diagnosis of adrenal insufficiency will be collected on a separate Adrenal Insufficiency Adverse Event CRF and should not be recorded on the Adverse Event CRF.

If a subject develops an adrenal insufficiency AE meeting the seriousness criterion ([Section 8.3.2](#)) or the definition of an adrenal crisis ([Table 2](#)), the Investigator should discuss with Medical Monitor. In cases where a clear explanation for the occurrence of adrenal insufficiency or adrenal crisis is identified, discontinuation of the study medication is not necessary. If there is no clear explanation for serious event of adrenal insufficiency, then PI may discuss further steps with medical monitors.

If the subject develops adrenal insufficiency due to undertreatment (as opposed to an acute stressor), the subject's daily GC dose should be increased by 5 mg HCe and should not be reduced again to the GC dose level associated with adrenal insufficiency (per Investigator judgment and discussion with the Medical Monitor). Study drug should not be discontinued but may be interrupted while GC dose adjustment is made.

In the absence of any clear explanation for the subject's acute adrenal insufficiency, the Investigator should discontinue study drug. This will be considered an AESI (see [Section 8.3.8](#)).

Adverse events or other conditions that lead to GC stress dosing should not be reported as AEs of adrenal insufficiency since the stress dosing is done to prevent, not treat, adrenal insufficiency.

7.1.6 Reproductive Hormone Stopping Criteria

If a subject experiences significant changes from baseline in reproductive hormone(s), the Investigator should determine whether such changes represent clinically significant reproductive abnormalities, potential risks to the subject, whether to discontinue study drug, and appropriate safety follow-up. These changes include but are not limited to significant changes in LH, FSH, or SHBG; significant changes in inhibin B or testicular dysfunction in men; and significant changes in estradiol, prolactin, progesterone, or menstrual cyclicity in women.

Investigators should keep in mind that subjects with CAH can be expected to have abnormal reproductive hormone levels because deficient 21-hydroxylase enzyme activity leads 1) to elevated levels of cortisol precursors that are shunted into reproductive hormone biosynthetic pathways and 2) to low levels of the cortisol that normally provides negative feedback on the HPA axis. Standard-of-care therapy with GC and mineralocorticoid replacement does not necessarily fully normalize adrenal steroid production pathways and signaling systems, including ACTH and CRF levels. Thus, subjects with CAH can be expected to have abnormal plasma concentrations of various androgens and progestogens at baseline. Therapy with an effective CRF receptor antagonist may in fact shift the balance between various intermediates in the steroid biosynthetic pathway. Investigators should inform the Medical Monitor before discontinuing study drug.

7.1.7 Clinically Significant Adverse Event Stopping Criteria

The Investigator should consider study drug discontinuation and appropriate safety follow-up for a subject who experiences a clinically significant AE. When feasible, the Investigator should contact the Medical Monitor to discuss the subject's clinical condition before discontinuing study drug. Clinically significant AEs include but are not limited to study drug-related SAEs ([Section 8.3.2](#)) and study drug-related AESIs ([Section 8.3.8](#)).

7.2 Participant Withdrawal from the Study

Subjects are free to withdraw from the study at any time upon request. If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before the withdrawal of consent. The subject may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Subjects will be withdrawn from the study by the Investigator and/or Sponsor for either of the following:

- Pregnancy
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject

A subject may also be withdrawn from the study by the Investigator and/or Sponsor at any time for other safety, behavioral, compliance, or administrative reasons such as the following:

- Significant protocol deviation or noncompliance with study procedures/restrictions
- If the subject no longer meets eligibility criteria
- Study termination by the Sponsor

Subject withdrawal is expected to be uncommon. If possible, an early termination visit (as shown in the Schedule of Post-Screening Activities in [Section 1.3.3](#)) should be conducted before subject withdrawal. The Investigator must document the date and primary reason for the withdrawal on the appropriate eCRF. Subjects who withdraw prematurely may be replaced at the discretion of the Sponsor to ensure adequate numbers of evaluable subjects.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if the subject repeatedly fails to attend scheduled visits and study personnel are unable to reach the subject.

The following actions must be taken if a subject fails to attend a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject, including, where possible, making 3 telephone calls to the subject and, if necessary, sending a certified letter to the subject's last known mailing address (or local equivalent methods). Attempts to contact the subject should be documented in the subject's medical record.
- If the subject continues to be unreachable, the subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

This section describes what study assessments and procedures will be performed and how they will be conducted. The timing of study assessments and procedures is provided in the Schedules of Activities in [Section 1.3](#).

8.1 Efficacy Assessments

8.1.1 Hormone Assessments

All blood samples will be collected at 8 AM (\pm 1 hour) prior to administering their GC dose after an overnight fast (nothing to eat after midnight) unless otherwise specified.

A4, 17-OHP, ACTH, and testosterone will be measured.

Detailed instructions for the collection and handling of biological samples will be provided separately.

8.1.2 Quality of Life Assessments

Quality of life will be measured using the SF-36, the Patient Global Impression of Change (PGIC), and the Clinical Global Impression – Improvement Scale (CGI-I).

8.1.2.1 Short Form 36

The SF-36 ([Ware and Sherbourne 1992](#)) is a widely used, validated, patient-reported survey that assesses subjective health status. The SF-36 consists of 36 items and the following 8 health domains: physical functioning, role-physical (limitations in usual role activities because of physical health problems), bodily pain, general health perceptions, vitality, social functioning, role-emotional (limitations in usual role activities because of emotional problems), and mental health. Domain scores range from 0 to 100, with higher scores corresponding to better subjective health status. The survey provides summary scores for physical health and mental health.

8.1.2.2 Patient Global Impression of Change

The PGIC ([Guy 1976](#)) is a 1-question survey that asks subjects to evaluate whether there has been an improvement in overall subjective health status. Subjects select a response on a 7-point Likert scale.

8.1.2.3 Clinical Global Impression – Improvement Scale

The CGI-I ([Guy 1976](#)) is a 1-question survey that requires the clinician to assess how much a patient's illness has improved or worsened relative to a baseline state. Clinicians select a response on a 7-point Likert scale.

8.1.3 Metabolic Assessments

A lipid panel (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides) and hemoglobin A1c (HbA1c), fasting glucose, and fasting insulin will be assessed as part of clinical laboratory (see [Section 13.3](#)). Homeostatic model assessment of insulin resistance (HOMA-IR) will be calculated from fasting glucose and fasting insulin. Blood pressure (systolic and diastolic) will be assessed. Body weight, BMI, and waist circumference will be assessed as described in [Section 8.2.3](#).

8.1.4 Hyperandrogenic Symptoms

8.1.4.1 Acne

Acne severity will be evaluated using an IGA score ([FDA 2018](#)). Qualified medical professionals will assess the IGA score.

Information regarding any concomitant medications for acne, including topical treatments, should be solicited from subjects.

8.1.4.2 Hirsutism

Hirsutism will be evaluated in female subjects using a mFG score ([Yildiz 2010; Martin 2018](#)). Qualified medical professionals will assess the mFG score. The mFG scores each of 9 body areas on a scale of 0 (no hair) to 4 (hairiness typical of a man), with the sum of the separate scores providing a hormonal hirsutism score.

Information regarding any concomitant medications or depilatory methods for hirsutism should be solicited from subjects.

8.1.4.3 Testicular Adrenal Rest Tumors

TARTs are a common complication of CAH caused by ACTH-driven overstimulation of aberrant adrenal cells within the testes ([Olpin and Witt 2014](#)) and may result in pain, discomfort, impaired spermatogenesis, and infertility ([Chihaoui 2016; Claahsen-van der Grinten 2014; Delfino 2012](#)). Complete scrotal ultrasounds will be obtained for male subjects using a real-time scanner to detect and to evaluate the size and number of TARTs. Standard images should be obtained in the longitudinal and transverse planes. Each potential TART lesion will be measured in 3 planes to allow for calculation of TART volume. Detailed instructions for performing the scrotal ultrasound will be provided separately.

The initial scrotal ultrasound may be scheduled for any time up to the Week 4 visit and will be considered the baseline measurement for the TART endpoint. Only subjects with a TART at baseline will be followed for TART changes. Scrotal ultrasounds will be read by a central radiologist blinded to treatment assignment and to the study timepoints at which ultrasounds were taken.

8.1.4.4 Menstrual Cyclicity

Female subjects will record menstrual information in their electronic study diaries, including the start and stop dates of menses.

8.2 Safety Assessments

Safety assessments will include monitoring and recording all AEs (including SAEs, AEs leading to discontinuation/withdrawal, and AESIs), physical examination, vital signs assessment, ECGs, clinical laboratory, monitoring for suicide risk, and depression/anxiety. AE procedures are described in [Section 8.3](#).

8.2.1 Physical Examination

A full physical examination should include assessments of the cardiovascular, respiratory, GI, neurological, and musculoskeletal systems; head, eyes, ears, neck, and throat (HEENT); thyroid; skin; and extremities. The full physical examination may exclude rectal, genitourinary, and breast exams.

An abbreviated physical examination should include the following components: cardiovascular, respiratory, abdomen, musculoskeletal, HEENT, and skin.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

A full physical examination will be performed during the Screening Visit and at Day 1, Week 18, and Week 76. If the physical exam is performed at the subject's home, the qualified medical professional will report any changes to the subject's health to the site to determine whether further evaluation is needed via an unscheduled visit.

8.2.2 Vital Signs

Vital signs consist of systolic and diastolic blood pressure, pulse rate, respiration rate, and body temperature. The subject should rest for at least 5 minutes before vital signs measurement without speaking or using a cellphone. The subject should ideally have an empty bladder. Vital signs will be measured as specified in the Schedules of Activities and as clinically indicated.

Blood pressure should be measured with an appropriately sized cuff on a bare arm just above the bend of the elbow. An appropriately sized cuff has the inflatable portion covering approximately 40% of the arm's circumference and the width of the cuff covering approximately 80% of the area from the elbow to the shoulder. The subject should be sitting in an upright position with feet flat on the floor and the measurement arm supported at heart level.

8.2.3 Body Weight, Height, BMI, and Waist Circumference

Body weight will be measured at every visit using a calibrated balance. The weight should be placed on a hard, flat surface and checked for zero balance before each measurement. The subject should stand unassisted, in the center of the platform, and be asked to look straight ahead, standing relaxed but still.

Height needs to be recorded at screening only.

BMI will be calculated for every visit using height and weight measurements.

Waist circumference will be measured using an appropriate tape measure placed horizontally just above the hip bones at the level of the belly button, placed snugly but not compressing the skin, and after the subject breathes out.

8.2.4 Electrocardiogram

A 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate, QRS, QT, and QTc intervals, preferably using Fridericia's formula. Any ECG measurement assessed by the Investigator as a clinically significant abnormality should be recorded in the AE section of the eCRF and monitored until resolution.

Refer to [Section 7.1.2](#) for QT individual treatment-stopping criteria and any additional ECGs that may be necessary.

8.2.5 Clinical Laboratory and Urinalysis

Clinical laboratory assessments include hematology, clinical chemistry, coagulation, lipid panel, thyroid panel, LH, FSH, SHBG, renin, aldosterone, inhibin B for males only, and estradiol, prolactin, and progesterone for females only. eGFR for screening will be calculated from blood creatinine measured as part of screening clinical chemistry.

A complete list of study-required clinical laboratory and urinalysis tests is provided in [Section 13.3](#).

All study-required clinical laboratory tests must be conducted in accordance with the laboratory manual and will be performed by a central laboratory.

The Investigator must review the laboratory report, document the review, and record any clinically significant laboratory findings that occur during the study in the AE section of the eCRF. Laboratory reports must be filed with the source documents. Clinically significant laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly during the Treatment Period or within 30 days after the last dose of study drug should be reported as AEs and repeated at least weekly until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

8.2.6 Psychiatric Evaluations

8.2.6.1 Columbia–Suicide Severity Rating Scale

The C-SSRS will be used during the study to monitor suicidal ideation and behavior. The C-SSRS is a Food and Drug Administration (FDA)–endorsed questionnaire administered by trained study personnel to screen for suicidality in trials of CNS-active compounds. The Baseline/Screening Version of the C-SSRS, which assesses both lifetime history and history from the last 12 months, will be used at screening to determine subject eligibility. The Since Last Visit Version of the C-SSRS will be used at all subsequent visits specified.

Refer to [Section 7.1.3](#) for suicidality individual treatment-stopping criteria.

8.2.6.2 Hospital Anxiety and Depression Scale

Subject anxiety and depression will be monitored during the study using the HADS, assessed at Weeks 6, 18, 30, 58, 70, and 76 ([Zigmond and Snaith 1983](#)). The HADS is a widely used subject-reported instrument that focuses on subjective disturbances of mood rather than physical signs. The scale consists of 14 items, 7 items each for anxiety and depression. Each item is rated on a 4-point scale based on the frequency of symptoms over the preceding week and ranging from 0 (not at all) to 3 (very often).

Refer to [Section 7.1.4](#) for depression and/or anxiety individual treatment-stopping criteria.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a clinical trial subject who has signed the ICF; the event need not necessarily have a causal relationship with the study drug. Examples of AEs include but are not limited to:

- Clinically significant abnormal test results
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Progression/worsening of underlying disease

A treatment-emergent adverse event (TEAE) is an AE that is temporally associated with administration of study drug and is defined as an AE that occurs during or after administration of the first dose of study drug of the Treatment Period until 30 days after the final dose of study drug (safety follow-up visit). For AEs that occur on the date of the first dose of study drug of the Treatment Period, the time of onset (before or after intake of study drug) must be specified.

An abnormal test result should be reported as an AE if any of the following criteria are met:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in study drug dosing or study drug discontinuation, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the Investigator or Sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Examples of events that do not meet the definition of an AE include but are not limited to:

- Clinically significant abnormal test result or other abnormal safety assessment associated with the underlying disease, unless it is more severe than expected for the subject's condition
- The underlying disease and its signs and symptoms, unless they are more severe than expected for the subject's condition
- Medical and surgical procedures; the condition that leads to the procedure is the AE if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment for the AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

8.3.2 Definition of Serious Adverse Event

An SAE or serious adverse drug reaction is any untoward medical occurrence at any dose that meets any of the following criteria:

- Results in death
- Is life threatening (immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events include allergic bronchospasm that requires intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

Hospitalization does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (eg, caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Same-day surgeries (as outpatient/same day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include the following:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for workup of persistent pre-treatment lab abnormality)
- Social admission (eg, subject has no place to sleep)
- Administrative admission (eg, for yearly physical exam)
- Protocol-specified admission during a clinical trial (eg, for a procedure required by the trial protocol)
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery)
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

8.3.3 Classification of an Adverse Event

As far as possible, each AE will be described by the following:

- Duration (start and end dates)
- Severity ([Section 8.3.3.1](#))
- Relationship to study drug ([Section 8.3.3.2](#))
- Action(s) taken and, as relevant, the outcome ([Section 8.3.3.3](#))

8.3.3.1 Severity

The Investigator will assess the severity of each AE according to the National Cancer Institute CTCAE version 5.0 ([CTCAE 2017](#)), which is summarized in [Table 4](#).

Table 4. Severity of Adverse Events

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

Abbreviations: ADL, activities of daily living; AE, adverse event.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. Severe is a category used for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met at least one of the criteria for an SAE listed in [Section 8.3.2](#), such as resulting in hospitalization.

If there is a change in the severity of an ongoing AE, it will be recorded as part of the same event, with the worst grade of severity for the entire event timeframe being recorded.

8.3.3.2 Relationship to Study Drug

The Investigator will assess the relationship of each AE to study drug (or HC stress dosing) according to the categories in [Table 5](#). This assessment will serve to determine whether there exists a reasonable possibility that the study drug (or HC stress dosing) caused or contributed to the AE.

Table 5. Relatedness of Adverse Event to Study Drug (or HC Stress Dosing)

<p>UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).</p>
<p>UNLIKELY RELATED: This category applies to those AEs that are judged to be unrelated to the study drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to the study drug if or when it <u>meets two of the following criteria</u>:</p> <p>(1) it does not follow a reasonable temporal sequence in relation to administration of the study drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) it does not follow a known pattern of response to the study drug; or (4) it does not reappear or worsen when the study drug is re-administered.</p>
<p>POSSIBLY RELATED: This category applies to those AEs for which a connection to study drug administration cannot be ruled out with certainty. An AE may be considered possibly related if or when it <u>meets two of the following criteria</u>:</p> <p>(1) it follows a reasonable temporal sequence in relation to administration of study drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; or (3) it follows a known pattern of response to the study drug.</p>
<p>PROBABLY RELATED: This category applies to those AEs that the Investigator thinks are related to the study drug with a high degree of certainty. An AE may be considered probably related if or when it <u>meets three of the following criteria</u>:</p> <p>(1) it follows a reasonable temporal sequence in relation to administration of the study drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) it disappears or decreases on cessation or reduction in dose of study drug. There are exceptions when an AE does not disappear upon discontinuation of the study drug yet drug-relatedness clearly exists (eg, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the study drug.</p>
<p>DEFINITELY RELATED: This category applies to those AEs that the Investigator thinks are incontrovertibly related to the study drug. An AE may be assigned an attribution of definitely related if or when it <u>meets all of the following criteria</u>:</p> <p>(1) it follows a reasonable temporal sequence in relation to administration of the study drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) it disappears or decreases upon cessation or reduction in dose of study drug and recurs with re-exposure to the study drug (if re-challenge occurs); and (4) it follows a known pattern of response to the study drug.</p>

Abbreviation: AE, adverse event.

The Investigator will use clinical judgment and consult the IB to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug (or HC stress dosing) administration will be considered and investigated.

AEs classified as unrelated or unlikely related will be considered not related to treatment, and AEs classified as possibly, probably, or definitely related will be considered related to treatment.

8.3.3.3 Outcome

The outcome of each AE will be recorded as one of the categories in [Table 6](#).

Table 6. Outcome of Adverse Event

Not recovered/not resolved: The event has not improved or recuperated.
Recovered/resolved: The event has improved or recuperated. The subject recovered from the AE. Record the AE stop date.
Recovering/resolving: The event is improving. No AE stop date should be recorded when an AE is recovering/resolving.
Recovered/resolved with sequelae: The subject recuperated but retained pathological conditions resulting from the prior disease or injury. Record the AE stop date. The AE stop date will represent the date the AE stabilized with no change in event outcome anticipated.
Unknown: There is an inability to access the subject or the subject's records to determine the outcome (ie, subject withdraws consent or is lost to follow-up). No AE stop date should be recorded.
Fatal: The AE directly caused death. Record the date of death as the AE stop date.

Abbreviation: AE, adverse event.

8.3.4 Time Period and Frequency for Event Assessment and Follow-up

AEs will be recorded from the time the ICF is signed until the end of the follow-up period. AEs will be assessed at each study visit, and subjects should be encouraged to contact the study site to report AEs that occur between scheduled visits. AEs that occur in the time period between informed consent and the first dose of study drug of the Treatment Period should be recorded but will not be considered TEAEs. If the AE occurs on the date of the first dose of study drug of the Treatment Period, the time of onset (before or after intake of study drug) will be captured.

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event has been shown to be unrelated to study drug, or the subject is lost to follow-up (as defined in [Section 7.3](#)).

8.3.5 Adverse Event Reporting

The Investigator is to report all AEs, whether volunteered by the subject, discovered through questioning, or directly detected, that occur in the time period specified in [Section 8.3.4](#) and according to classifications described in [Section 8.3.3](#).

Non-serious AEs that don't require immediate reporting are to be reported on the AE eCRF.

SAEs and AESIs will receive special consideration in decisions about continuing, modifying, or suspending dosing/enrollment. The Investigator will notify the Sponsor within 1 day of awareness for immediate review (see [Section 8.3.6](#)).

8.3.6 Serious Adverse Event Reporting

Throughout the study, the Investigator is to report all SAEs, regardless of suspected causality, to the Sponsor within 24 hours of learning of its occurrence using the SAE Report Form in the EDC system. AESIs (see [Section 8.3.8](#)) will also be reported on the SAE Report Form in the EDC system and must be clearly differentiated from SAEs. Completion guidelines are provided in the Investigator Site File. The Investigator must assess and record the relationship of each event to study drug. Any SAE experienced after the follow-up period should be reported to the Sponsor only if the Investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE, regardless of when they occur, must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. Follow-up information will also be captured in the EDC system and should describe whether the event resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported SAE should be reported separately as a new event.

The Sponsor will ensure that all suspected unexpected serious adverse reactions (SUSARs), determined based on the Reference Safety Information in the most recent version of the IB at the time of the event, will be reported to the competent authorities of all countries where the trial is performed and to all IRBs/ECs overseeing the conduct of the study, in accordance with FDA 21 CFR 312.32 and European Directive 2001/20/EC. These reports will be unblinded upon submission where required.

8.3.7 Reporting of Pregnancy

Any subject who becomes pregnant during the study will have study drug discontinued immediately and be withdrawn from the study. All pregnancies in female subjects or in the female partners of male subjects must be reported to the Sponsor within 24 hours of the site learning of the pregnancy. Information about pregnancies will be recorded on the Pregnancy Report Form and any follow-up information will be forwarded to the Sponsor.

For any female subject who becomes pregnant while participating in this study, the Investigator will collect information about the pregnancy and follow up with the subject to determine the outcome of the pregnancy and the status of mother and child.

Male subjects will be instructed to notify the site in the event that any female partner becomes pregnant. If any female partner of a male subject who received at least 1 dose of study drug becomes pregnant within 90 days of the male subject's last dose of study drug, the Investigator will attempt to collect information about the pregnancy. The Investigator must obtain informed consent from the pregnant partner before collecting such information. The Investigator will also attempt to follow up with the female partner to determine the outcome of the pregnancy and the status of mother and child.

Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Pregnancy in itself is not regarded as an AE. However, a pregnancy complication is an AE, and congenital abnormalities/birth defects or spontaneous miscarriages should be reported as SAEs. Elective termination of a pregnancy is not considered an AE. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of such an SAE through spontaneous reporting.

8.3.8 Adverse Events of Special Interest

AESIs must be monitored on an ongoing basis. These events will be reported with narratives, allowing for the collection of additional information, as warranted. The following may be considered AESIs for this study:

- Significant liver chemistry changes that do not satisfy study drug stopping rules (see [Section 7.1.1](#) and [Section 13.2](#)). Cases of Hy's Law should be reported as SAEs.
- Suicidality as indicated by Type 3, 4, or 5 ideation on the C-SSRS (see [Section 7.1.3](#) regarding study drug stopping criteria for suicidality and [Section 8.2.6.1](#) regarding the C-SSRS). This safety finding will be reported as an AESI if it is not considered an SAE (eg, resulting in hospitalization).
- Depression or anxiety that is moderate or severe (CTCAE Grade 2 or higher), as assessed by the Investigator (see [Section 7.1.4](#) regarding study drug stopping criteria for depression or anxiety). This will be reported as an AESI if it is not considered an SAE (eg, resulting in hospitalization).
- Adverse events of adrenal insufficiency will be reported on a separate Adrenal Insufficiency Form. Additionally, symptoms of adrenal insufficiency will be reported as SAE if they necessitate parental GC administration by a health care professional and two of the following criteria are met: hypotensive (systolic blood pressure <100 mmHg); nausea or vomiting; severe fatigue; documented hyponatremia, hyperkalemia, or hypoglycemia. If hospitalization was required or the event of adrenal insufficiency is deemed to be an important medical event, life-threatening, results in a persistent or significant disability/incapacity or death, it should also be reported as an SAE.
 - For SAEs of adrenal insufficiency, records from the office of health care provider, emergency facility or hospital the following information should be obtained as source documents to provide the following information:
 - Was stress dosing employed prior to the adrenal insufficiency event? If yes, what were the GC dose and duration of dosing and the cause for stress dosing prior to seeking medical attention?
 - What type, dose and route of parental GC was administered and the duration of administration?
 - What concomitant medications were administered?
 - What clinical laboratory results are available?
 - What AEs occurred?
 - What was the duration of stay if admitted to the hospital?
 - What was deemed to be the inciting factor leading to adrenal crisis?

For non-SAEs of adrenal insufficiency, all symptoms and findings on physical examination, vital sign collection and/or laboratory assessments leading to the diagnosis of adrenal insufficiency will be collected.

Adverse events or other conditions that lead to GC stress dosing should not be reported as AEs of adrenal insufficiency since the stress dosing is done to prevent, not treat, adrenal insufficiency. If an AE, such as an infection, results in GC stress dosing, the AE should be captured in the Adverse Event CRF. The following additional information will be collected in the patient diary during episodes of GC stress dosing: start and stop date, concomitant medications, cause for stress dosing (eg, infection, strenuous exercise, emotional stress, pain, surgery) and concurrent AEs. Adverse events resulting in the stress dosing will be reported on the Adverse Event CRF.

8.4 Pharmacokinetic Assessments

A plasma sample will be collected consistently by a qualified medical professional at 8 AM (\pm 1 hour) for measurement of tildacerfont concentration at each study visit indicated in the Schedule of Post-Screening Activities. Samples will be collected after an overnight fast (nothing to eat after midnight) and before subjects take any morning dose of GC. Tildacerfont drug concentration will be determined by a bioanalytical laboratory using validated methods.

9 STATISTICAL CONSIDERATIONS

Statistical considerations are summarized here. A detailed description of statistical methods will be provided in the Statistical Analysis Plan (SAP).

9.1 Statistical Hypotheses

For the Primary Efficacy Analysis, the null hypothesis is that there is no difference in the profile of log A4 change from baseline through 12 weeks of blinded randomized treatment between tildacerfont and placebo. The alternative hypothesis is that there is difference in the profile of log A4 change from baseline through 12 weeks of blinded randomized treatment between tildacerfont and placebo.

9.2 Sample Size Determination

A sample size of n=15 subjects per group will provide at least 80% power to detect a difference of at least 50% in A4 mean percent change from baseline between a given dose level of tildacerfont and placebo, assuming a common SD of 30%.

An assumed dropout rate of 15% during the Treatment Period results in a target of 18 subjects per group and a total sample size of 72 subjects who enter the Treatment Period.

9.3 Populations for Analyses

The ITT Population will include all randomized subjects regardless of Treatment Period eligibility or completion. The ITT Population will be the primary analysis set for analyzing demographics, baseline characteristics, and efficacy analyses.

The mITT Population is all randomized subjects who receive at least 1 dose of study drug (tildacerfont or placebo), have at least 1 post-baseline A4 assessment, and did not change background GC through Week 18

The PP Population for each part of the Treatment Period will include all eligible subjects who have no major protocol deviations that would affect the analysis of efficacy data (defined below). The PP Population may be used for secondary analyses of the primary and secondary efficacy endpoints. Additional criteria for the PP Population may be specified in the SAP. The PP Population will be identified prior to database lock.

Major protocol deviations that would affect the analysis of efficacy data are defined as the following:

- Subject did not meet efficacy-based inclusion criteria (elevated biomarkers)
- Subject met efficacy-based exclusion criteria (use of dexamethasone, night-shift worker)
- Subject's drug compliance was <80% over the Treatment Period

Additional criteria may be specified in the SAP.

The Safety Population will include all subjects who receive at least 1 dose of study drug (tildacerfont or placebo) during the Treatment Period, summarized by actual drug received. The Safety Population will be the primary analysis set for general and safety analyses.

The PK Population will include all randomized subjects who receive at least 1 dose of tildacerfont and have at least 1 evaluable PK sample.

9.4 Statistical Analyses

9.4.1 General Considerations

All individual data will be listed as measured. All statistical summaries and analyses will be performed using SAS software (SAS Institute Inc, Cary, North Carolina, USA).

Continuous data will be summarized using an 8-point descriptive summary (n, mean, SD, median, IQR [25% quartile, 75% quartile], minimum, and maximum) or 7-point descriptive summary (n, mean, SD, CV, median, minimum, and maximum) unless otherwise specified.

Categorical data will be summarized using the frequency of events and percentage of total events.

Baseline definitions for each endpoint will be defined in the SAP.

Data will be presented by treatment group. Changes in primary, secondary, and exploratory endpoints will be analyzed over time, with change from baseline summarized for each post-baseline time point measured.

All efficacy analyses will be conducted on the ITT Population using a 2-sided alpha of 0.05. The primary endpoint and secondary endpoints will be reported using a multiplicity algorithm.

Efficacy analyses at Week 18 (primary and secondary) will compare tildacerfont treatment groups to placebo. Efficacy analyses at Week 76 will evaluate change from baseline only.

For missing data, a retrieved dropout approach will be used in which missing endpoint data for subjects who discontinued early will be imputed using data collected from subjects after discontinuation of study drug.

Any changes to the protocol-specified analyses will be pre-specified in the SAP prior to database lock.

9.4.2 Analysis of the Primary Efficacy Endpoint

The primary objective of the study is to evaluate the effect of tildacerfont in controlling A4 levels in adult subjects with classic CAH who have elevated biomarkers at baseline on their current, dose of GC replacement therapy over the 12-week, double-blind, placebo-controlled Part A of the Treatment Period. This objective will be achieved via A4 dose response analysis. The null hypothesis is that there is no difference in the profile of log A4 change from baseline through 12 weeks of blinded randomized treatment between tildacerfont and placebo. The alternative hypothesis is that there is difference in the profile of log A4 change from baseline through 12 weeks of blinded randomized treatment between tildacerfont and placebo. Statistical testing for dose response will be performed using the repeated measures random coefficients mixed-effects model.

A sensitivity analysis of the primary endpoint may be conducted using a missing data-handling procedure.

9.4.3 Analysis of the Secondary Efficacy Endpoints

9.4.3.1 Proportion Who Achieve Hormone Target Secondary Endpoints

The secondary efficacy analyses related to A4 will be achieved as an integral part of the dose response modelling. The secondary efficacy analyses related to 17-OHP will be conducted using the same methodology as the primary efficacy analysis

Additional proportion-based analyses may be specified in the SAP. Missing values for proportion endpoints will not be imputed and will be assumed to be failures.

Additionally, changes in biomarkers will be summarized by timepoint as appropriate, mean-based or geometric-mean based analyses. Subjects meeting specific thresholds as specified in the SAP, eg, \leq ULNs, will also be summarized.

9.4.3.2 Testicular Adrenal Rest Tumor Endpoints

The secondary endpoint, change in TART lesion volume at Week 18, will be analyzed using an ANCOVA model with baseline lesion size as a covariate and fixed effects for randomization strata and treatment. Additional covariates may be specified in the SAP.

The exploratory endpoint, change in TART lesion volume at Week 76, will be analyzed using a repeated measure mixed effects model with treatment and visit as fixed effects, subject as a random effect, and the baseline score as a covariate. Additional covariates may be specified in the SAP.

9.4.4 Analysis of the Exploratory Efficacy Endpoints

9.4.4.1 Testicular Adrenal Rest Tumor Endpoints

The exploratory endpoint, change in TART lesion volume at Week 18, will be analyzed using an ANCOVA model with baseline lesion size as a covariate and fixed effects for randomization strata and treatment. Additional covariates may be specified in the SAP.

The exploratory endpoint, change in TART lesion volume at Week 76, will be analyzed using a repeated measure mixed effects model with treatment and visit as fixed effects, subject as a random effect, and the baseline score as a covariate. Additional covariates may be specified in the SAP.

9.4.4.2 Correlation of Tildacerfont Plasma Concentration vs Dose

The correlation of tildacerfont plasma concentration versus dose will be explored by presentation of PK descriptive statistics by dose and scheduled time point (i.e., study Week 10 and 18).

9.4.4.3 Correlation of A4 Level vs 17-OHP Level

The within subject correlation OF a4 vs 17-OHP will be assessed on the log scale by randomized treatment arm. The estimated correlation coefficient will be extracted from a variance-covariance matrix and presented by randomized treatment arm.

9.4.4.4 Patient- and Clinician-Reported Outcomes Endpoints

Changes in SF-36 total score, IGA acne score, and mFG hirsutism score will be analyzed using a repeated measure mixed effects model with treatment (two covariates: randomized and group at Week 76) and visit as fixed effects, subject as a random effect, and the baseline score as a covariate if >2 timepoints are assessed. If only the baseline timepoint and a single post-baseline timepoint are assessed for the endpoint, an ANCOVA model with the baseline score as a covariate will be used with only a single treatment covariate (randomized treatment). There will be no imputation of missing data.

9.4.4.5 Glucocorticoid Dose Reduction Endpoints

The proportion of subjects with at least a 5 mg/day HCe reduction from baseline in GC dose and A4 \leq ULN at Week 76 will be summarized using an exact score test through logistic regression using the randomization strata and treatment group at Week 76 in the model specification. Missing values for proportion endpoints will not be imputed and will be assumed to be failures. Additional covariates may be specified in the SAP.

Additional GC-related proportions, eg, proportion of subjects at specific dose levels, may be specific in the SAP.

9.4.5 Analysis of the Exploratory Efficacy Endpoints in the Optional Open-Label Extension Period

The percent change from baseline in GC dose at EOT will be summarized descriptively.

The proportion of subjects with GC dose \leq 25 mg/day in HCe and A4 \leq ULN at EOT will be summarized descriptively.

The proportion of male subjects with reduction in TART(s) at EOT who had TART(s) at baseline will be summarized descriptively.

The proportion of subjects with improvement in at least one cardiovascular risk factor at EOT will be summarized descriptively and will comprise the following cardiovascular risk factors, weight, waist circumference, BMI, HOMA-IR, systolic and diastolic blood pressure, cholesterol and LDL. Thresholds for improvement will be specified the SAP. Additional cardiovascular risk factors may be specified in the SAP.

9.4.6 Safety Analyses

The Safety Population will be used for all safety analyses. All safety data will be presented in listings. Summary tables will be provided for concomitant medications, AEs, hematology and chemistry laboratory results, vital signs, and ECG findings. Safety data will be summarized by treatment group using frequency of event or descriptive statistics, as appropriate.

9.4.6.1 Extent of Exposure

Dosing information for individual subjects will be listed. Using dosing data, estimates of exposure to tildacerfont will be summarized. Dose discontinuations and reasons for study drug discontinuation will be listed and summarized.

9.4.6.2 Concomitant Medication Data

Concomitant medications used before and during the Treatment Period will be summarized.

9.4.6.3 Adverse Event Data

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AE summaries will be presented by System Organ Class, Preferred Term, severity, and frequency and percentage of subjects reporting each observed event.

AEs that occur before the first dose of study drug of the Treatment Period will be distinguished from TEAEs (defined in [Section 8.3.1](#)). All AEs and TEAEs will be listed by subject. The frequency of subjects who experience TEAEs will be summarized overall and by treatment group. TEAEs will also be summarized by relationship to study drug and severity.

Listings will be provided for subjects who experienced an SAE or discontinued study drug/withdrew from the study because of an AE.

9.4.6.4 Laboratory Data

Clinical laboratory test results will be listed by subject. Reference ranges provided by the laboratory for each parameter will be used to evaluate the clinical significance of laboratory test results. Values outside the relevant reference range will be flagged in the listings. Abnormal clinical laboratory test results will be listed in a separate listing.

Laboratory data will be summarized in terms of observed values, changes from baseline, values relative to normal ranges, and changes from baseline relative to normal ranges. Subjects meeting specific thresholds for laboratory data will also be summarized as specified the SAP.

P-values for change from baseline and change from placebo or differences in proportions meeting specific thresholds will be derived using t-tests as specified in the SAP.

Additional subgroup analyses based on baseline laboratory data [elevated, normal] will be specified in the SAP.

9.4.6.5 *Vital Signs Data*

Vital signs data will be summarized within appropriately defined categories in terms of observed values (by time point), changes from baseline (by time point), and counts and percentages. Subjects meeting specific thresholds for vital signs data will also be summarized as specified the SAP.

P-values for change from baseline and change from placebo will be derived using t-tests as specified in the SAP.

9.4.6.6 *Electrocardiogram Data*

The QTcF, PR interval, QT interval, QRS duration, and heart rate from standard digital ECGs will be summarized within appropriately defined categories in terms of observed values, changes from baseline, and counts and percentages.

9.4.6.7 *Psychiatric Evaluations*

C-SSRS and HADS data will be listed.

9.4.7 *Baseline Descriptive Statistics*

Demographics and baseline characteristics (including age, sex, race, ethnicity, height, weight, and BMI) will be summarized for the ITT Population.

Biomarkers at screening and at baseline will be summarized for the Safety Population.

Baseline clinical characteristics and history will be summarized.

9.4.8 *Subgroup Analyses*

The following pre-defined subgroups will be analyzed:

- Baseline A4 [≤ 4 x ULN, >4 x ULN]
- Baseline HCe dose [≤ 30 mg/day, >30 mg/day]
- Sex [male, female]
- Age [≤ 30 years, >30 years]; [\leq median, $>$ median]

Any additional subgroup analyses will be specified in the SAP.

9.5 Primary and Final Analyses

The primary analysis is planned after all subjects have completed Week 18. The Sponsor and CRO will be unblinded to treatment assignment in Part A at the time of the primary analysis, but Investigators, who conduct the study, and subjects will remain blinded.

The final analysis will occur after the last subject has completed the last follow-up visit or if the study is discontinued by the Sponsor.

A clinical study report will be completed for the study with results up to Week 76/80. An addendum to the clinical study report will be completed to summarize the results from Week 76 up to Week 316/320.

9.6 Multiplicity Control

The primary endpoint (percent change from baseline in A4 after 12 weeks on treatment [Week 18]) and secondary endpoints (proportion of subjects who achieve A4 \leq ULN after 12 weeks on treatment [Week 18], proportion of subjects who achieve 17-OHP \leq 1200 ng/dL after 12 weeks on treatment [Week 18], and change in the lesion volume of TART(s) from baseline after 12 weeks on treatment [Week 18]) will be reported under strict control of the Type I error using a multiplicity algorithm which will be detailed in the SAP.

9.7 Data Monitoring Committee

Refer to [Section 10.6 \(Safety Oversight\)](#) for information on the Data and Safety Monitoring Board (DSMB).

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Informed Consent

For each study subject, written informed consent must be obtained before the subject may be enrolled into the study and before any protocol-specified procedures may be conducted. The signing of the ICF must also be witnessed where required by law or regulation. The ICF will also be signed and dated by the Investigator and/or designee. The process of obtaining informed consent should be documented in the subject source documents. Each study subject will be provided a copy of his/her signed and dated ICF.

As part of the informed consent process, the Investigator or designee must explain to each subject the purpose and procedures of the study and the possible risks involved. Subjects should be informed that they may withdraw from the study at any time. They should be informed that their data will be stored in a confidential manner, in accordance with local data protection laws. They should be informed that their records may be viewed by the Sponsor or its designee and by regulatory authorities. The ICF and any other materials provided to subjects or investigative staff must use vocabulary and language that can be readily understood.

The Investigator must use the most current IRB/EC-approved ICF. Any changes to the proposed ICF suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB/EC, and a copy of the approved version must be provided to the Sponsor after IRB/EC approval.

10.2 Study Discontinuation and Closure

Premature study termination may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or Sponsor decision. In addition, the Sponsor retains the right to discontinue development of tildacerfont at any time.

Premature study termination will occur if the benefit/risk profile becomes unfavorable because of a new risk or toxicity that makes the study unjustifiable and/or if new scientific evidence that could affect subject safety becomes available during the study (e.g., from other clinical trials). When AEs occur, the Sponsor will evaluate the severity, duration, frequency, and nature of the AEs relative to the existing safety profile of tildacerfont to determine whether there are any substantial changes in risk-benefit considerations.

If this study is prematurely terminated or discontinued, the Sponsor will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects within 7 days and have them complete final visit safety assessments. As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

10.3 Confidentiality and Privacy

All information obtained during the conduct of this study will be regarded as confidential, and written permission from the Sponsor is required before disclosing any information related to this study.

All processing of personal data at the site and by the Sponsor must be carried out in accordance with any legislation concerning the protection of personal data. The Investigator must ensure that the subject's privacy is maintained. The Sponsor will assign each subject a unique identifier. Any subject records or datasets that are transferred from the site to the Sponsor will contain this identifier only; subject names or any information that would make the subject identifiable will not be transferred.

10.4 Future Use of Stored Specimens and Data

Any biological samples collected for this study may be stored for up to 5 years after the last study visit of the last subject in the study. These samples may be used in the future for the discovery, analysis, verification, and/or validation of other biomarkers or tests related to CAH. Samples will not directly identify subjects on the label. Consent from subjects to store the samples will be requested, and subjects may elect to opt out of prolonged sample storage at any time by indicating so in the ICF. A record of the final disposition of subject samples will be maintained by the Sponsor.

10.5 Key Roles and Study Governance

10.5.1 Sponsor

The Sponsor or its designee will provide protocol training to investigative staff as appropriate. Clinical monitors will conduct site visits as needed to ensure study procedures are conducted in accordance with the protocol, GCP, and all applicable regulatory requirements. Throughout the study, a Sponsor representative will be available to address any issues that may arise.

A list of study contacts will be provided in a separate document.

10.5.2 Investigators

Before study start, Investigators are required to sign an Investigator Protocol Agreement Page confirming their agreement to conduct the study in accordance with the protocol. It is the responsibility of the Investigator to ensure that all investigative personnel are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

10.5.3 Institutional Review Board/Ethics Committee

The protocol and ICF must be reviewed and approved by a properly constituted IRB/EC before study start. A signed and dated statement that the protocol and ICF have been approved by the IRB/EC must be given to the Sponsor before study initiation.

10.6 Safety Oversight

An external, independent DSMB will review the available safety data from this study periodically and provide recommendations to the Sponsor if needed. The DSMB will be composed of independent reviewers who are not involved in the conduct of the study and will include at least 1 endocrinologist, 1 hepatologist, and 1 statistician. The DSMB will review both blinded and unblinded safety data and advise the Sponsor of any trends or safety issues that may impact the study or study subjects. The Sponsor will make final decisions concerning the continuation, modification, or termination of the trial. The DSMB's scope of responsibility, membership, confidentiality, and procedures will be established in a separate DSMB charter.

10.7 Clinical Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, adherence to the protocol and to GCP, the progress of enrollment, and that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. See [Section 11.4](#) for information on monitoring visits in the context of COVID-19 or other logistical challenges.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with eCRF entries. The Sponsor's monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of subjects will be disclosed.

Refer to [Section 10.9.1](#) for information on eCRFs and source documents.

10.8 Quality Assurance and Quality Control

In addition to routine clinical monitoring by the Sponsor, the study may be evaluated by Sponsor internal auditors and government inspectors, who must be allowed access to case report forms, source documents, and other study files. Sponsor audit reports will be kept confidential. The Investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to the Sponsor.

10.9 Data Handling and Record Keeping

10.9.1 Data Collection and Management Responsibilities

An eCRF must be completed for each enrolled subject. Completed original case report forms are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor. It is the Investigator's responsibility to ensure completion of and to review and approve all eCRFs. Case report forms must be signed by the Investigator. These signatures serve to attest that the information contained on the eCRFs is true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs.

For each subject in the study, the Investigator must maintain source documents at the trial site consisting of the original ICF signed by the subject (a copy of which is given to the subject), the hospital/clinic or physician medical records/chart for the subject, case and visit notes, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. In some cases, certain items entered on the eCRF may not require a separate written record, and the eCRF itself may serve as the source document. Such items will be prospectively defined between the Sponsor and Investigator before study start.

10.9.2 Study Records Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor or its designees, the Investigator agrees to keep records that include the identity of all subjects (sufficient information to link records [eg, eCRFs and hospital records]), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and treatment disposition. The records should be retained by the Investigator for as long as ICH, local regulations, or the Clinical Study Agreement dictates, whichever is longer.

If the Investigator relocates, retires, or for any reason withdraws from the trial, the Sponsor should be prospectively notified, and the trial records must be transferred to an acceptable designee, such as another Investigator, another institution, or the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

10.10 Protocol Deviations

If a protocol deviation occurs that affects a subject's safety, the Sponsor must be informed as soon as possible.

If a protocol deviation is implemented to eliminate an immediate hazard before a protocol amendment can be submitted for IRB/EC review and approval/favorable opinion (see [Section 10.12](#)), the deviation will be reported as soon as possible to 1) the IRB/EC for review and approval/favorable opinion, 2) the Sponsor, and 3) regulatory authority(ies), if required by local regulations. Documentation of approval signed by the chairperson or designee of the IRB(s)/EC(s) must be sent to the Sponsor.

10.11 Publication and Data Sharing Policy

Any manuscripts for publication based on data from this study must be submitted to the Sponsor for review and comment before submission to a publisher. This requirement should not be construed as a means of restricting publication but is intended solely to ensure concurrence regarding data, evaluations, and conclusions and to provide an opportunity for the Sponsor to share with the Investigator any new or unpublished information of which the Investigator may be unaware.

10.12 Amendments

The study shall be conducted as described in this protocol. All revisions to the protocol must be discussed with and prepared by the Sponsor. The Investigator should not implement any change to the protocol without a prior protocol amendment that has been reviewed by and received documented approval/favorable opinion from the IRB/EC, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant protocol deviation must be documented (see [Section 10.10](#)).

If a protocol amendment is an Administrative Letter, Investigators must inform their IRB(s)/EC(s).

If a protocol amendment substantially alters the study design or increases the potential risk to the subject, 1) the consent form must be revised and submitted to the IRB(s)/EC(s) for review and approval/favorable opinion, 2) the revised consent form must be used to obtain re-consent from subjects currently enrolled in the study if they are affected by the amendment, and 3) the revised consent form must be used to obtain consent from any new subjects prior to enrollment.

11 COVID-19 RISK MITIGATION

11.1 Risk/Benefit Assessment in the Context of COVID-19 or Other Logistical Challenges

In general, the CAH patient population possesses a higher-than-average risk of serious complications from any infection or febrile illness because such conditions can lead to adrenal crises in CAH patients if they are not managed appropriately. The emergence of COVID-19 increases the overall infection risk in affected communities, including CAH patients who reside in those communities.

Participation in a clinical trial provides subjects with increased access to healthcare resources and reinforcement of appropriate practices during a time of increased infection risk. Study participants will have access to healthcare professionals on a more intensive schedule than in normal clinical practice for the management of CAH. The standard of care for a CAH patient with an infection or febrile illness is to increase the patient's GC dose to accommodate the additional stress and prevent an adrenal crisis (see

[Section 6.5.1.5](#)). The Sponsor will provide HC for stress dosing to all subjects during the study, starting at the beginning of the Run-in Period. Thus, study participants will have immediate access to supplemental GC in the event of COVID-19 or other infection.

The potential risks of a subject receiving tildacerfont and concomitantly developing COVID-19 have been considered. Tildacerfont is not expected to increase the risk of contracting a viral illness such as COVID-19 or to increase the risk of severe illness with COVID-19.

11.2 Study Conduct in the Context of COVID-19 or Other Logistical Challenges

All study activities will be conducted in accordance with relevant local, regional, and national guidance around COVID-19.

If in-clinic visits are no longer possible, in-clinic-only activities (eg, scrotal ultrasound) will not be conducted. After a site reopens or the shelter-in-place order is lifted, attempts should be made to conduct any missed in-clinic activities via an unscheduled visit.

If a subject or a member of the subject's household is suspected or confirmed to have COVID-19, the Investigator must consult with the Medical Monitor to determine the best course of action. In this situation, only telemedicine activities can proceed. If the subject misses scheduled study activities during this time, an unscheduled visit will be conducted once the subject or member of his/her household no longer has suspected or confirmed COVID-19. At a minimum, safety labs must be performed at the unscheduled visit. Subjects cannot go more than 3 months or 2 consecutive scheduled visits without labs being drawn.

For scenarios not delineated here or for further clarification, the Investigator should consult with the Medical Monitor to determine the best course of action.

11.3 Subject Disposition in the Context of COVID-19 or Other Logistical Challenges

If a subject develops an active COVID-19 infection (whether confirmed or suspected) during the course of the study, the Investigator will work with the subject and the Medical Monitor to determine the best course of action, taking into consideration the AE and SAE guidelines in [Section 8.3](#) and the individual stopping criteria for clinically significant AEs in [Section 7.1.7](#). If study drug is discontinued or a subject is withdrawn from the study because of COVID-19, the reason for early termination will be captured in the EDC system as such.

11.4 Regulatory and Study Oversight Considerations in the Context of COVID-19 or Other Logistical Challenges

If planned onsite monitoring visits are not possible because of COVID-19, remote monitoring may occur, if allowed by local and federal legal and regulatory requirements. If source data are collected at a home health visit, those source documents will be maintained with the home healthcare staff until they can be transferred to the trial site. If a protocol deviation is the result of COVID-19-related circumstances, this information should be captured.

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13 APPENDICES

13.1 Appendix of Prohibited Concomitant Medications

Refer to [Section 6.5.2](#) for more information on prohibited concomitant medications.

Because of their potential impact on the metabolism of tildacerfont, moderate to strong CYP3A4 inducers and inhibitors are prohibited. Subjects will be advised to refrain from consumption of grapefruit, grapefruit juice, or any fruits that are known to be strong CYP3A4 inhibitors from 1 day before the first dose of study drug until after the final dose.

In addition, drugs that are sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 and/or BCRP must be avoided. Sensitive substrates or narrow-therapeutic-range substrates of BCRP that are not also metabolized by CYP3A4 and that can be administered QD in the morning (separated by approximately 10 hours from evening administration of study drug) may be permitted with monitoring for safety.

Ethinyl estradiol is a CYP3A4 and BCRP substrate, and tildacerfont may increase the level of ethinyl estradiol by <1.25-fold. With ethinyl estradiol doses $\leq 35 \mu\text{g}$, exposure to ethinyl estradiol is unlikely to reach the threshold associated with increased thromboembolic or cardiovascular risk that is observed with higher-dose ethinyl estradiol formulations. Thus, any hormonal contraception containing ethinyl estradiol used by female subjects must contain $\leq 35 \mu\text{g}$ ethinyl estradiol, is permitted only for subjects who would not be considered at high risk for thromboembolic or cardiovascular complications with estrogen use, and must be used simultaneously with a backup method of contraception according to [Section 5.2.5.2](#). Dosing of oral formulations of hormonal contraception containing ethinyl estradiol should be offset by approximately 10 hours from the evening dose of study drug.

The following is a non-exhaustive list of medications that are prohibited because of their potential for metabolic interactions with tildacerfont. This list is intended to show more commonly encountered drugs that subjects may be taking at screening. Any drugs of concern should be discussed with the Medical Monitor.

alfentanil	darifenacin	itraconazole	phenobarbital	simvastatin
apixaban	diltiazem	ketoconazole	phenytoin	St John's wort
atorvastatin	elagolix	lesinurad	posaconazole	teneligliptin
avanafil	eletriptan	loperamide	quetiapine	ticagrelor
avasimibe	ethinyl estradiol ($>35 \mu\text{g}$)	lovastatin	repaglinide	triazolam
buspirone	felodipine	mibepradil	rifampin	vardenafil
carbamazepine	fluconazole	midazolam	rifapentine	voriconazole
cenobamate	glyburide	nefazodone	rivaroxaban	
ciprofloxacin	isavuconazole	oseltamivir	sildenafil	

Many oncology drugs and medications used to treat the hepatitis C virus and HIV are strong inhibitors of CYP3A4 but are not listed above simply because individuals with active cancer, hepatitis C, and/or HIV are excluded from this study.

13.2 Appendix of Liver Safety

Liver chemistry stopping criteria are presented in [Section 7.1.1](#).

13.2.1 Suggested Actions, Follow-up Assessments, and Monitoring When Liver Chemistry Stopping Criteria Are Met

13.2.1.1 Actions

- Immediately discontinue study drug.
- Within 24 hours, report the event to the Sponsor or designated CRO and complete the AE eCRF (indicating that it is an AESI).
- If the event also meets the criteria for an SAE (see [Table 3](#)), complete the SAE fields in the eCRF.
- Request list of any medications taken in last 48 hours. Specifically question about medications that are known to increase liver enzymes, such as aspirin, acetaminophen, ibuprofen, naproxen, diclofenac, phenylbutazone, and any antibiotics.
- Perform liver chemistry follow-up assessments (see [Section 13.2.1.2](#)).
- Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see [Section 13.2.1.3](#)).
- If restart/rechallenge is not granted, permanently discontinue study drug and continue participant in the study for any protocol-specified follow-up assessments.

13.2.1.2 Follow-up Assessments

- Perform viral hepatitis serology: hepatitis A immunoglobulin M (IgM) antibody, hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb), hepatitis C RNA, cytomegalovirus IgM antibody, Epstein-Barr viral capsid antigen IgM antibody (or, if unavailable, heterophile antibody or monospot testing), and hepatitis E IgM antibody.
- Obtain blood sample for PK analysis. Record on the eCRF the date/time of the PK blood sample draw and the date/time of the last dose of study drug before the blood sample draw. If the date or time of the last dose is unclear, provide the subject's best approximation. Instructions for sample handling and shipping will be provided in the laboratory manual from the applicable central laboratory.
- Measure serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Obtain complete blood count with differential to assess eosinophilia.

- Record the appearance or worsening of clinical symptoms of liver injury or hypersensitivity on the AE report form.
- Record use of concomitant medications (including acetaminophen, herbal remedies, and other OTC medications) on the concomitant medications eCRF.
- Record alcohol use in EDC according to eCRF completion guidelines.

For a possible Hy's Law case (ALT \geq 3x ULN AND total bilirubin \geq 2x ULN or INR $>$ 1.5):

- Fractionate bilirubin if total bilirubin is \geq 2x ULN.
- Measure anti-nuclear antibody, anti-smooth muscle antibody, type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins.
- Perform serum acetaminophen adduct high-performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury) in subjects with definite or likely acetaminophen use in the preceding week.
- Perform liver imaging (ultrasound, magnetic resonance, or computerized tomography) of complete liver and/or liver biopsy to evaluate liver disease.

13.2.1.3 Monitoring

For a possible Hy's Law case (ALT \geq 3x ULN AND total bilirubin \geq 2x ULN or INR $>$ 1.5):

- Repeat liver chemistry tests (include ALT, AST, ALP, GGT, bilirubin, total bile acids, PT/INR, and PTT) and perform liver event follow-up assessments within **24 hours**.
- Collect blood samples twice weekly for repeat liver chemistry tests (ALT, AST, ALP, GGT, bilirubin, total bile acids, PT/INR, and PTT) until abnormalities resolve, stabilize, or return to baseline.
- A specialist or hepatology consultation is recommended.

For a non-Hy's Law case of ALT \geq 3x ULN that meets other liver chemistry stopping criteria:

- Repeat liver chemistry tests (include ALT, AST, ALP, GGT, bilirubin, total bile acids, PT/INR, and PTT) and perform liver event follow-up assessments within 24 to 72 hours.
- Collect blood samples weekly for repeat liver chemistry tests (ALT, AST, ALP, GGT, bilirubin, total bile acids, PT/INR, and PTT) until abnormalities resolve, stabilize, or return to baseline.

13.2.2 Increased Liver Chemistry Monitoring While Continuing Study Drug

If ALT \geq 3x ULN and $<$ 5x ULN **and** total bilirubin $<$ 2x ULN, **without** symptoms believed to be related to liver injury or hypersensitivity, **and** the subject can be monitored weekly for 4 weeks, perform the following actions:

- Notify the Medical Monitor within **24 hours** of learning of the abnormality to discuss subject safety.
- Subject can continue study drug.

- Collect blood samples weekly for repeat liver chemistry tests (ALT, AST, ALP, GGT, bilirubin, total bile acids, PT/INR, and PTT) until the abnormalities resolve, stabilize, or return to baseline.
- If at any time the subject meets liver chemistry stopping criteria, proceed as described in [Section 7.1.1](#) and [Section 13.2.1](#).
- If, after 4 weeks of monitoring, ALT <3x ULN and total bilirubin <2x ULN, monitor per standard scheduling for remainder of study and follow-up period.

13.2.3 Restart Following Transient Resolving Liver Chemistry Events Not Related to Study Drug

The Investigator may request the Sponsor to consider restarting study drug in a subject who stopped study drug because of a liver chemistry event. Approval for study drug restart can be considered under the following circumstances:

- Liver chemistry events have a clear underlying cause (eg, biliary obstruction, pancreatic events, hypotension, acute viral hepatitis), liver chemistry tests have improved to normal or are within 1.5x baseline, and ALT <3x ULN.
- Possible drug-induced liver injury (DILI) has been excluded by the Investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study medication has an identified genetic marker associated with liver injury (eg, lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study drug-related liver injury cannot be excluded, the guidance on appropriate action and follow-up in the previous sections of this Appendix will apply.
- There is no evidence of alcoholic hepatitis.
- Medical Monitor approval of study drug restart has been obtained.

If restart of study drug is approved by the Sponsor in writing:

- Study drug must be administered at the dose specified by the Sponsor.
- Subjects approved by the Sponsor for restart of study drug must have twice weekly blood draws for liver chemistry tests until stable liver chemistry tests have been demonstrated, and then standard laboratory monitoring may resume as per protocol.
- If the subject meets protocol-defined liver chemistry stopping criteria after study drug restart, study drug should be permanently discontinued.
- The Medical Monitor must be informed of the outcome for the subject following study drug restart.
- The Sponsor must be notified of any AEs.

13.3 Appendix of Clinical Laboratory and Urinalysis Tests

Refer to [Section 8.2.5](#) for more information on clinical laboratory and urinalysis tests.

Laboratory Assessments	Parameters	
Hematology	Platelet count	
	RBC count	
	RBC indices: MCV, MCH, % reticulocytes	
	Hemoglobin	
	Hematocrit	
WBC count		
	Differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils	
Clinical Chemistry ¹	Potassium	ALP
	Calcium	ALT/SGPT
	Sodium	AST/SGOT
	BUN	GGT
	Creatinine	Total and direct bilirubin
	Total protein	Total bile acids
Coagulation	PT/INR, PTT	
Lipid Panel	Total cholesterol, LDL, HDL, triglycerides	
Thyroid Panel	T3 (free and total), T4 (free and total), TSH	
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, by dipstick Microscopic examination (if blood or protein is abnormal)	
Other Tests	LH, FSH, SHBG, renin, aldosterone	
	For males only: inhibin B	
	For females only: estradiol, prolactin, progesterone	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; LH, luteinizing hormone; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; SAE, serious adverse event; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone; ULN, upper limit of normal; WBC, white blood cell.

¹ Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in [Section 7.1.1](#) and [Section 13.2](#). All events of ALT ≥ 3 x ULN plus total bilirubin ≥ 2 x ULN ($>35\%$ direct bilirubin) or ALT ≥ 3 x ULN plus INR >1.5 may indicate severe liver injury (possible Hy's Law) and must be reported as SAEs.

13.4 Appendix Regarding Genetic Sample Collection and Testing

Where local regulations permit and subject to discretionary approval from each site's IRB/EC and to subject consent, a voluntary blood sample may be collected for DNA analysis. These samples may be tested for CAH genotype, genes related to the mechanism of action of tildacerfont, and drug metabolism enzyme and transporter polymorphisms. Drug metabolism enzyme and transporter polymorphisms may be evaluated using an analytical methodology that comprehensively assesses an array of drug metabolism enzyme and transporter genes from a single sample. Alternative genotyping platforms may be used, if appropriate, to confirm initial results. Certain genotyping may be omitted at the discretion of the Investigator and/or Sponsor (eg, if the subject was previously tested for certain genes using the same platform/technology). No additional testing will be performed on these samples.

Details regarding the collection, processing, storage, and shipping of samples can be found in the Laboratory Manual. Samples collected as part of a later analysis will be securely stored in a central biorepository selected by the Sponsor for up to 5 years after the last study visit of the last subject in the study, or as local regulations allow. Any samples remaining after 5 years will be destroyed.