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

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Investigational Medicinal Product:	SPR001 (tildacerfont)
Indication:	Classic congenital adrenal hyperplasia (CAH)
Sponsor:	Spruce Biosciences, Inc. 611 Gateway Blvd. Suite 740 South San Francisco, CA 94080 United States
Registries:	ClinicalTrials.gov: NCT04544410 EudraCT #: 2019-004765-40 EU CT#: 2023-503771-13-00

SPONSOR APPROVAL PAGE

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This protocol has been reviewed and approved by Spruce Biosciences, Inc.:

DocuSigned by:
Saba Sile
714FA14B8C454FF...

16-Apr-2024

Saba Sile, MD — Date

Vice President, Clinical Development

DocuSigned by:
Abe Castro
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Abe Castro — Date

Executive Director, Clinical Development Operations

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

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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: _____

_____ _____

Principal 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
BMD	bone mineral density
BMI	body mass index
BSAP	bone-specific alkaline phosphatase
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
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
CTCAE	Common Terminology Criteria for Adverse Events
CTX-1	C-terminal telopeptide of type 1 collagen
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DXA	dual-energy X-ray absorptiometry

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
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
LLD	lower limit of detection
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MCID	minimum clinically important differences
MedDRA	Medical Dictionary for Regulatory Activities
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
TID	3 times daily
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
U-NTx	urinary N-linked telopeptide of type 1 collagen
WBC	white blood cell
wc	waist circumference

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Study Number: SPR001-204

Study Title

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

Study Phase: IIb

Study Rationale

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 adrenocorticotropic 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.

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 (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 CRF type 1 (CRF_1) 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.

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.

SPR001-204 is a randomized, double-blind, placebo-controlled study that will evaluate the potential of tildacerfont to reduce GC burden in adult subjects with classic CAH who have lower limit of detection (LLD) ≤ A4 ≤ 2.5x upper limit of normal (ULN) and are on supraphysiologic doses of GC therapy (≥30 mg/day and ≤60 mg/day in hydrocortisone [HC] equivalents [HCe]). SPR001-204 will be the first study of tildacerfont to evaluate GC dose reduction. In addition, Study SPR001-204 will characterize clinical outcomes after up to 76 weeks of treatment with tildacerfont. An optional Open-Label Extension Period will provide additional open-label treatment with tildacerfont at 200 mg QD for up to 240 weeks.

Objectives	**Endpoints**
Efficacy	
Primary Efficacy	
To evaluate the mean absolute GC change in subjects with CAH over the 24-week, Double blind, Placebo-Controlled Treatment period	Absolute change from baseline in GC dose in HCe at Week 24
Secondary Efficacy	
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels while maintaining androgen control in subjects with CAH	Proportion of subjects with GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or A4 ≤ ULN at Week 24
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels while maintaining androgen control in subjects with CAH	Proportion of subjects with baseline GC dose ≤ 35mg HCe who achieve GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or ≤ ULN at Week 24
To evaluate the effect of tildacerfont in reducing cardiovascular risk in subjects with CAH	Proportion of subjects with improvement in at least one cardiovascular risk factor at Week 24
Exploratory Efficacy	
To evaluate the percentage change in GC use in subjects with CAH	Percent change from baseline in GC dose at Week 24

To evaluate the effect of tildacerfont in reducing the cumulative HCe dose in subjects with CAH	Change in total cumulative GC dose in HCe at Week 24
To evaluate the effect of tildacerfont in improving HOMA-IR in subjects with CAH	Change from baseline in the HOMA-IR at Week 24
To evaluate the effect of tildacerfont in improving HOMA-IR after 52 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in HOMA-IR after 52 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont in reducing cardiovascular risk in subjects with CAH	Proportion of subjects with improvement in at least one cardiovascular risk factor at Week 52
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels while maintaining androgen control in subjects with CAH	Proportion of subjects with GC dose ≤ 11 mg/m2/day and A4 ≤ 1.2x baseline or ≤ ULN at Week 52
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels while maintaining androgen control in subjects with CAH	Proportion of subjects with baseline GC dose ≤ 35mg HCe who achieve GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or ≤ ULN at Week 52
To evaluate the effect of tildacerfont in improving quality of life (QoL) in subjects with CAH	Change from baseline at Week 24 in the Short Form 36 (SF-36) total score
To evaluate the effect of tildacerfont in improving quality of life (QoL) in subjects with CAH	Change from baseline at Week 52 in the SF-36 total score
To evaluate the effect of tildacerfont on BMI after 24 weeks in subjects with CAH	Percent change from baseline in BMI at Week 24
To evaluate the effect of tildacerfont on BMI after 52 weeks of tildacerfont treatment in subjects with CAH	Percent change from baseline in BMI after 52 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont on waist circumference (wc) after 24 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in waist circumference after 24 weeks of tildacerfont treatment

To evaluate the effect of tildacerfont on waist circumference (wc) after 52 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in wc after 52 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont in improving body composition after 24 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in fat mass and fat/lean mass percentage ratio after 24 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont in improving body composition after 52 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in fat mass and fat/lean mass percentage ratio after 52 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont in improving bone mineral density (BMD) after 52 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in BMD after 52 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont in reducing TART(s) in male CAH subjects with TART(s) at baseline after 24 weeks of tildacerfont treatment in subjects with CAH	Proportion of male subjects with reduction in TART volume at Week 24 who had TART(s) at baseline
To evaluate the effect of tildacerfont in reducing TART(s) in male CAH subjects with TART(s) at baseline after 52 weeks of tildacerfont treatment in subjects with CAH	Proportion of male subjects with reduction in TART volume at Week 52 who had TART(s) at baseline
To evaluate the effect of tildacerfont in reducing GC use while maintaining normal A4 levels at Week 24 in subjects with CAH	Proportion of subjects with at least a 5 mg/day HCe reduction from baseline (Day 1) in GC dose and A4 ≤ 1.2x baseline or ≤ ULN at week 24
To evaluate the effect of tildacerfont in reducing GC use while maintaining normal A4 levels at Week 52 in subjects with CAH	Proportion of subjects with at least a 5 mg/day HCe reduction from baseline (Day 1) in GC dose and A4 ≤ 1.2x baseline o ≤ ULN at week 52
Exploratory Efficacy (Optional Open-Label Extension Period)	
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels in subjects with CAH	Proportion of subjects with GC dose ≤11 mg/m2/day in HCe and A4 ≤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 improving BMD in subjects with CAH	Change from baseline in BMD 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 volume 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 2-part treatment period that will evaluate the potential of tildacerfont to reduce GC burden in adult subjects with classic CAH who have LLD ≤ A4 ≤ 2.5x ULN and are on supraphysiologic doses of GC therapy (≥30 mg/day and ≤60 mg/day in HCe). The first 24 weeks of the treatment period will be a randomized, double-blind, placebo-controlled study in which subjects are randomized in a 1:1 ratio to receive either placebo or tildacerfont at 200 mg once daily (QD). All subjects will receive open-label tildacerfont at 200 mg QD during the remaining 52 weeks of the treatment period. An optional Open-Label Extension Period will provide an 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:

- A ≤45-day *Screening Period* for confirmation of eligibility
  - Optional A4 Screening Visit
  - Screening information captured within 45 days of the start of Day 1 in this study (particularly screening information transferred from Spruce Biosciences Study SPR001-203 to this study) will be used to determine eligibility and fulfill screening requirements for this study.

In Germany, screening information from Spruce Biosciences Study SPR001-203 is not permitted to be transferred to determine study eligibility.

- A 6 or 12-week *Glucocorticoid Conversion Period* (Week -12 to either Week -6 or Week -2 [±3 days]) for subjects on dexamethasone at the initial Screening Visit who agree to convert to a non-dexamethasone regimen as determined by their physician.
- A 76-week, 2-part *Treatment Period*
    - The 24-week *Placebo-Controlled Treatment Period* (Day 1 to Week 24) will be randomized, double-blind, and placebo-controlled. Subjects will be randomized in a 1:1 ratio to receive either placebo or tildacerfont at 200 mg QD.
    - The 52-week *Open-Label Period* (day after Week 24 to Week 76) will provide subjects who complete the Placebo-Controlled Treatment Period with 52 weeks of open-label treatment with tildacerfont 200 mg QD.
    - Beginning at Week 2 (based on the Day 1 A4 measurement), subjects with an A4 measurement ≤ULN at a study visit will begin to reduce their daily GC dose in increments of no more than 5 mg/day HCe each time, down to a minimum of 15 mg HCe per day. Beginning at Week 6 (based on Week 6 A4 measurement), subjects with an A4 >1.25x ULN will begin to increase their daily GC dose by increments of no more than 5 mg/day HCe each time. More details on GC dose adjustments are provided in Section 4.1.4.3.
    - Subsequent GC dose adjustments are based on A4 measurements at Weeks 12, 18, 24, 32, 40, 52 and 64.
- 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 4.1.4.3).
- A 30-day *Follow-up Period at EOT*
    - Subjects who do not continue to the Open-Label Extension Period upon completion of Treatment Period 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.

Study Visit Schedule

- During the Screening Period:
    - Optional A4 Screening Visit
    - Screening Visit at ≤45 days before Day 1

- During the Glucocorticoid Conversion Period (for subjects on dexamethasone at Screening): visits at Weeks -12 and -8 (and -2, if applicable); scheduled telephone contacts at Weeks -11 and -6 (and -5, if applicable)
- During the 24-week Placebo-Controlled Treatment Period: visits on Day 1 (Baseline) and at Weeks 3, 6, 12, 18, and 24
- During the 52-week Open-Label Period: visits at Weeks 32, 40, 52, 64, and 76; scheduled telephone contacts at Weeks 27 and 46
- 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. 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 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), 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 during the Glucocorticoid Conversion Period at Weeks -11 and -6 (and -5, if applicable) and during the Treatment Period at Weeks 27 and 46 to record any AEs and concomitant medications.

After receiving A4 results from the Day 1 (dose reduction only) and Week 6, 12, 18, 24, 32, 40, 52, and 64 study visits, as well as visits in the optional Open-Label Extension Period, sites will make telephone contacts to subjects who are eligible for a GC dose adjustment. Sites will contact these subjects within 2 weeks after each applicable study visit. 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 GC 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 Glucocorticoid Conversion and Treatment Periods, subjects will use an electronic study diary to document study drug and background GC adherence. Female subjects will also use the study diary to record menstrual information (including start and stop dates of menses).

Study Population

This study will randomize approximately 90 subjects with classic CAH currently receiving GC at a supraphysiologic dose (defined under Eligibility Criteria). 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, dexamethasone (or a combination of the aforementioned GCs)
3. Has LLD ≤ A4 ≤ 2.5x ULN at screening measured before AM GC dose
4. Has been on a stable, supraphysiologic dose of GC replacement (defined as ≥30 mg/day and ≤60 mg/day in HCe) for ≥1 month before screening
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 CRF_1 receptor antagonist
4. Shows clinical signs or symptoms of adrenal insufficiency
5. 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 m^2
    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
6. 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 baseline (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 baseline
7. 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
8. Routinely works overnight shifts
9. 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.
10. Females who are pregnant or nursing

11. Use of any other investigational drug from 30 days or 5 half-lives (whichever is longer) before screening to the end of the study
12. Use of the following drugs from 30 days or 5 half-lives (whichever is longer) before the start of the Treatment Period 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)
13. 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 CRF_1 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

At the beginning of the Placebo-Controlled Treatment Period, subjects will be randomized in a 1:1 ratio to receive either placebo or tildacerfont at 200 mg QD for 24 weeks. During the Open-Label Period, all subjects will receive open-label tildacerfont at 200 mg QD for 52 weeks. During the optional Open-Label Extension Period, subjects will continue to receive tildacerfont at 200 mg QD. Study drug will be taken 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.

Subjects entering the study under protocol version 7.0 will use a Principal Investigator-prescribed supply of GCs. Subjects who entered the study under prior protocol versions will continue to use the GCs provided by the Sponsor through Week 24. After Week 24, subjects will use Principal Investigator-prescribed supply of GCs. Subjects will continue to use the same type of GC throughout the study. Please see important details on GC use in Section 4.1.4.1.

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 4.1.4.4). 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-Controlled Treatment Period of 24 weeks, an Open-Label Period of 52 weeks, and a safety follow-up period of approximately 30 days. Subjects who require the GC Conversion Period will participate for an additional 6 or 12 weeks. Subjects who continue in the optional Open-Label Extension Period will participate for up to an additional 240 weeks.

Statistical Analyses

Statistical Hypotheses

Efficacy endpoints at Week 24 will be evaluated using the following hypothesis-testing schema: The tildacerfont treatment group will be compared with the placebo treatment group. The null hypothesis is that there is no difference in the mean change from baseline to Week 24 in GC dose in HCe. The alternative hypothesis will be that there is a difference between the treatment groups.

Efficacy endpoints after 52 weeks of tildacerfont treatment will be evaluated using the following hypothesis-testing schema: The Week 52 value will be compared with the baseline value. The null hypothesis will be that there is no difference between the Week 52 and baseline values. The alternative hypothesis will be that there is a difference.

Sample Size

A sample size of N=45 subjects per group will provide at least 90% power to detect a between group difference in the proportion of subjects with at least a 5 mg/day HCe reduction from baseline in GC dose at Week 24 with A4 ≤ULN of at least 33% assuming the placebo group has a response of 30% and the two-sided type I error is 0.05.

Analysis Populations

- The Intent-to-Treat (ITT) Population will include all randomized subjects.
- The modified ITT (mITT) Population will include all randomized subjects who receive at least 1 dose of study drug (tildacerfont or placebo).

- The Per Protocol (PP) Population will include all randomized subjects who have no major protocol violations 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).
- The Pharmacokinetics (PK) Population will include all 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

Unless otherwise specified, continuous adrenal biomarkers (A4, 17-OHP, ACTH) will be summarized using a 11-point descriptive statistics (i.e., n, mean, standard deviation [SD], median, 25% quartile [Q1], 75% quartile [Q3], minimum, maximum, geometric mean, geometric coefficient of variance [CV%], 95% confidence interval [CI] for geometric mean [including geometric mean ratio and its 95% CI]). Continuous data aside from (A4, 17-OHP and ACTH) will be summarized using an 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 using the ITT Population as the primary analysis set. The primary analysis and secondary analyses conducted at Week 24 will compare the tildacerfont treated group to the placebo group. Additional secondary and exploratory analyses that evaluate the change from baseline in all subjects after 52 weeks of tildacerfont treatment will combine the subjects randomized to tildacerfont Day 1 to Week 52 data with subjects randomized to placebo tildacerfont treatment data from Week 24 to Week 76.

The primary efficacy endpoint is the absolute change from baseline in GC dose in HCe at Week 24. The analysis of the primary endpoint will be summarized using an exact score test for binomial proportions, as appropriate, or a chi-square–based test. Subjects with missing data will be assumed to be failure for the primary endpoint.

GC dose endpoints will be summarized using an analysis of covariance (ANCOVA) model with fixed covariates for baseline GC dose and treatment group. Sensitivity analyses that use multiple imputation will be conducted for missing GC dose data. The factors impacting the multiple imputation will include, but not be limited to, sex and baseline HCe group (<40 mg/day and ≥40 mg/day).

The proportion of subjects meeting various responder definitions will be summarized in a similar manner as the primary endpoint.

Metabolic endpoints (HOMA-IR, body weight, and wc), QoL endpoint (SF-36), and BMD will be analyzed using a repeated measure mixed effects model with treatment and visit as fixed effects, subject as a random effect, and baseline score as a covariate if >2 timepoints are

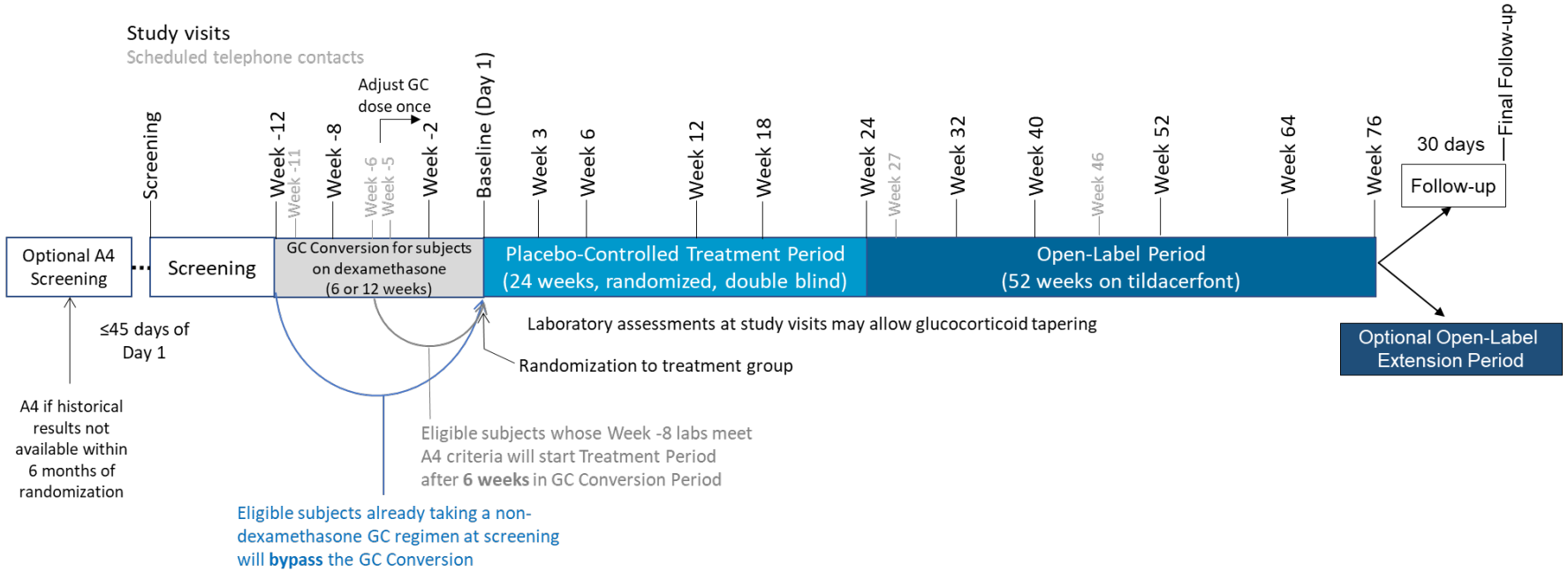
assessed. If only the baseline timepoint and a single post-baseline timepoint are assessed for the endpoint, an ANCOVA model with baseline as a covariate will be used. There will be no imputation of missing data.

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

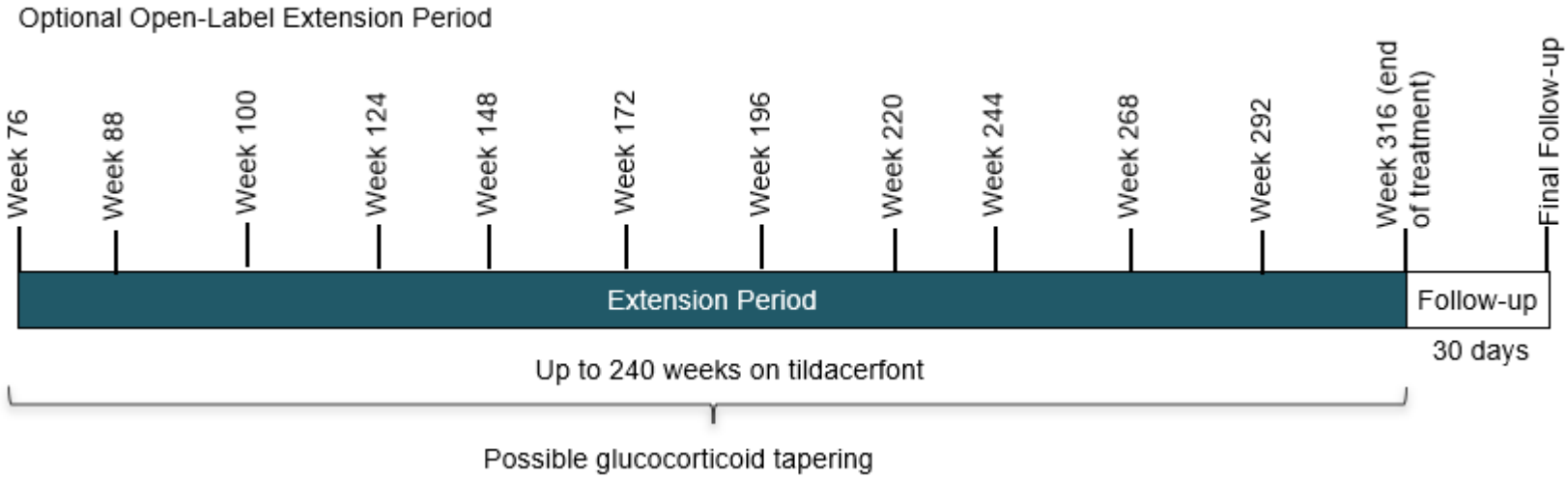
Safety Analyses

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



The 6or 12-week GC conversion only applies to subjects on dexamethasone at the initial Screening Visit who agree to convert to a non-dexamethasone regimen as determined by their physician.


Optional Open-Label Extension Period
Week 76
Week 88
Week 100
Week 124
Week 148
Week 172
Week 196
Week 220
Week 244
Week 268
Week 292
Week 316 (end of treatment)
Final Follow-up
Extension Period
Follow-up
30 days
Up to 240 weeks on tildacerfont
Possible glucocorticoid tapering

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 SPR001-204 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.

In Germany, Italy, and Poland the Screening Visit will be completed in the clinic ≤45 days before Day 1 of the study.

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 SPR001-203 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.

In Germany, screening information from Spruce Biosciences Study SPR001-203 is not permitted to be transferred to determine study eligibility.

	Screening Period	
STUDY VISIT NUMBER	**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]
Informed consent	X	X
Inclusion/exclusion criteria		X
Demography		X
Medical history		X
Prior medications from past year		X
Concomitant medications		X

	Screening Period	
STUDY VISIT NUMBER	**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]**
Prior and current GC regimens[2]		X
Vital signs[3], body weight		X
Height		X
Waist circumference		X
Full physical examination		X
C-SSRS		X
HADS		X
Hepatitis B & C and HIV tests		X[4]
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, adrenocorticotropic 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 SPR001-203) will be used to determine eligibility and fulfill screening requirements for this study. (In Germany, screening information from Spruce Biosciences Study SPR001-203 is not permitted to be transferred to determine study eligibility.)

[2] Subjects must be on a stable, supraphysiologic dose of GC replacement (defined as ≥30 mg/day and ≤60 mg/day in HCe) 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. (In Germany, Italy, and Poland, the Screening Visit will be performed in the clinic.)

[5] A4 and 17-OHP will be measured. The blood draw for 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, total and direct 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 Glucocorticoid Conversion Period Activities

The Glucocorticoid Conversion Period is required for subjects who require conversion from dexamethasone to a non-dexamethasone GC regimen.

	Glucocorticoid Conversion Period [1]						
	1st 6 weeks				**2nd 6 weeks, if GC dose adjustment necessary**		
STUDY VISIT NUMBER	**2**		**3**				**4**
STUDY WEEK	**-12**	**-11**	**-8**	**-6**		**-5**	**-2**
STUDY DAY [2]	**-84**	**-77**	**-56**	**-42**	**GC dose adjustment**	**-35**	**-14**
Visit Window (days)		**±3**	**±3**	**±3**		**±3**	**±3**
Study Visit (V)/ Telephone Contact (T)	**V**	**T**	**V**	**T**		**T**	**V**
Urine pregnancy test for FCP	X						
Hormones from blood [3,4]	X		X				X
Hematology [3]			X				X
Clinical chemistry [3]	X [5]		X				X
Renin [3]	X		X				X
Vital signs [6], body weight	X		X				X
GC accountability and return of used GC to site	X		X				X
Report subject's status to site	X		X				X
Concomitant medications	X	X	X	X		X	X
Monitor background GC dosing	X [7]	X	X	X		X	X
Determine whether subject requires GC dose adjustment/2nd 6 weeks OR can proceed to Treatment Period				X			
Background GC accountability			X				X
Dispense HC for stress dosing and perform accountability [8]	X		X				X
Review study diary/GC adherence [9]	X	X	X	X		X	X
Review adverse events	X	X	X	X		X	X
Physical examination (abbreviated)	X		X				X

Abbreviations: 17-OHP, 17 hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; EDC, electronic data capture; ET, early termination; FCP, female of childbearing potential; GC, glucocorticoid; T, telephone contact; V, study visit.

[1] If a subject fails to meet eligibility criteria or cannot tolerate the non-dexamethasone GC regimen during or at the end of the Glucocorticoid Conversion Period, the investigational site will schedule an abbreviated ET Visit to review AEs and concomitant medications and perform an abbreviated physical examination (preferably in the clinic but also permissible via home visit). (In Italy and Poland, the physical exam will not be performed at the subject's home and must be performed in the clinic).

[2] Study days are numbered relative to Day 1 (Week 0), the first day of the Treatment Period, when the subject will take the first dose of study drug. There is no Day 0 (ie, study days go directly from Day -1 to Day 1).

[3] Samples for these lab assessments will be obtained at 8 AM (± 1 hour), after an overnight fast (nothing to eat since the previous 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.

[4] A4, 17-OHP, ACTH, testosterone, and background GC levels will be measured.

[5] Total bile acids will not be included in clinical chemistry at the Week -12 visit.

[6] 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.

[7] On the first day of the Glucocorticoid Conversion Period, subjects will discontinue their dexamethasone GC regimen and begin taking a non-dexamethasone GC regimen.

[8] Bottles of HC for stress dosing (see Section 4.1.4.4) will be dispensed starting at the beginning of the Glucocorticoid Conversion Period and thereafter as needed to replace opened bottles. Accountability for bottles of HC will be performed at every study visit.

[9] Subjects will use an electronic study diary to document background GC adherence. Female subjects will also use the study diary to record menstrual information (including start and stop dates of menses).

1.3.4 Schedule of Treatment Period and Follow-up Activities

	Treatment Period													Follow-up[1]	ET
	Placebo-Controlled Treatment Period						Open-Label Period								
STUDY VISIT NUMBER	**5 Baseline**	**6**	**7**	**8**	**9**	**10**		**11**	**12**		**13**	**14**	**15**	**16**	
STUDY WEEK	**0**	**3**	**6**	**12**	**18**	**24**	**27**	**32**	**40**	**46**	**52**	**64**	**76[2]**	**80**	
STUDY DAY[3]	**1**	**22**	**43**	**85**	**127**	**169**	**190**	**225**	**281**	**323**	**365**	**449**	**533**	**Last dose +30 days**	
Study Visit (V) / Telephone Contact (T)[4]	**V**	**V[5]**	**V**	**V**	**V**	**V**	**T**	**V**	**V**	**T**	**V**	**V**	**V**	**V**	**V**
Urine pregnancy test for FCP	X		X	X	X	X		X	X		X	X	X	X	X
Hormones from blood[6,7]	X		X	X	X	X		X	X		X	X	X	X	X
Clinical laboratory[6,8]	X	X	X	X	X	X		X	X		X	X	X	X	X
Urinalysis[6]	X					X					X		X		X
HbA1c, fasting glucose and insulin, HOMA-IR[6]	X					X					X		X		X
BSAP, P1NP, CTX-1, U-NTx, Osteocalcin	X					X					X		X		X
PK[6,9]		X	X	X		X					X		X	X	X
Genetic sample[10]	X														
Vital signs[11], body weight	X	X	X	X	X	X		X	X		X	X	X	X	X
Waist circumference	X					X					X		X		X
12-lead ECG	X			X		X					X		X	X	X
HADS	X			X		X					X		X		X
SF-36	X					X							X		X
PGIC						X							X		X
Study treatment accountability and return of used treatment to site	X	X	X	X	X	X		X	X		X	X	X		
Scrotal ultrasound for males	X[12]					X[13]							X[13]		X[13]

	Treatment Period													Follow-up[1]	ET
	Placebo-Controlled Treatment Period						Open-Label Period								
STUDY VISIT NUMBER	**5 Baseline**	**6**	**7**	**8**	**9**	**10**		**11**	**12**		**13**	**14**	**15**	**16**	
STUDY WEEK	**0**	**3**	**6**	**12**	**18**	**24**	**27**	**32**	**40**	**46**	**52**	**64**	**76[2]**	**80**	
STUDY DAY[3]	**1**	**22**	**43**	**85**	**127**	**169**	**190**	**225**	**281**	**323**	**365**	**449**	**533**	**Last dose +30 days**	
Study Visit (V) / Telephone Contact (T)[4]	**V**	**V[5]**	**V**	**V**	**V**	**V**	**T**	**V**	**V**	**T**	**V**	**V**	**V**	**V**	**V**
DXA scan for body composition and bone mineral density[14]	X					X					X		X		X
Inclusion/exclusion criteria	X														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X			X		X					X		X		X
CGI-I						X							X		X
Randomization to study drug	X														
Dispense study drug[15]	X		X	X	X	X		X	X		X	X			
Study drug accountability		X	X	X	X	X		X	X		X	X	X		X
Monitor background GC dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GC dose adjustment telephone contacts[16]	X		X	X	X	X		X	X		X	X			
Dispense HC for stress dosing and perform accountability[17]	X	X	X	X	X	X		X	X		X	X	X	X	X
Review study diary/drug adherence[18]	X	X	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	X	X
Physical examination[19]	X		X	X	X	X		X	X		X	X	X	X	X

Abbreviations: 17-OHP, 17hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSAP, bone-specific alkaline phosphatase; CGI-I; Clinical Global Impression – Improvement Scale; C-SSRS, Columbia–Suicide Severity Rating Scale; CTX-1, C-terminal telopeptide of type 1 collagen; DXA, dual-energy x-ray absorptiometry (scan); 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-glutamyltransferase; HADS, Hospital Anxiety and Depression Scale; HbA1c, hemoglobin A1c; HC(e), hydrocortisone (equivalents); HOMA-IR, homeostatic model assessment of insulin resistance; INR, international normalized ratio; IRB, Institutional Review Board; LH, luteinizing hormone; LLD, lower limit of detection; P1NP, procollagen type 1 N terminal propeptide; PGIC, Patient Global Impression of

Change; PK, pharmacokinetics; PRN, as needed; PROs, patient-reported outcome measures; PT, prothrombin time; PTT, partial thromboplastin time; SF-36, Short Form 36; SHBG, sex hormone–binding globulin; T, telephone contact; TART, testicular adrenal rest tumor; ULN, upper limit of normal; U-NTx, urinary N-linked telopeptide of type 1 collagen; V, study visit.

[1] Subjects who do not continue to the optional Open-Label Extension Period upon completion of the Treatment Period 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 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 must be completed within a ±33+6-day window after the indicated study days. The day of the baseline visit (and first dose of study drug) will be considered Day 1 (Week 0), and all other study days are counted relative to Day 1. There is no Day 0 (ie, study days go directly from Day -1 to Day 1).

[4] During scheduled telephone contacts, sites will record any AEs and concomitant medications. After receiving A4 results during the Treatment Period, sites will make telephone contacts to applicable subjects regarding GC dose adjustment (detailed later in this Schedule of Activities). Subjects should be instructed to telephone sites if they have any concerns about their health. Telephone contacts initiated by sites and telephone contacts initiated by subjects should be captured in the EDC system as “unscheduled” telephone contacts.

[5] This visit for safety assessments may be scheduled for any day of Week 3, for any time of day, at the subject’s convenience. Clinical laboratory can be measured at any time of day for this visit and need not occur before the morning dose of GC.

[6] 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.

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

[8] Clinical laboratory assessments include hematology, clinical chemistry (including liver function tests such as ALT, AST, ALP, GGT, total and direct 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.

[9] A single blood sample will be drawn for PK measurement at each specified visit.

[10] 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.

[11] 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.

[12] The initial scrotal ultrasound may be scheduled for any time before the first dose of study drug and will be considered the baseline measurement for TART.

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

[14] DXA scans should be performed for all subjects as indicated. The initial DXA scan may be scheduled for any time before the first day of study drug and will be considered the baseline measurement for the bone mineral density endpoint and body composition assessments. Subjects should not take calcium supplements within the 24 hours before a DXA scan.

[15] Either the subject will pick up study drug in the clinic or the clinic will ship 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. (In Denmark, UK, Ireland, Romania, Estonia or Turkey shipping of study drug directly from clinic to subject’s home is not permitted)

[16] 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 no more than 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 reductions may

begin at Week 2 (based on the Day 1 A4 measurement) and increases in GC dose may begin based on the A4 measurement at Week 6. GC dose may be reduced to a minimum of 15 mg HCe per day (approximately physiologic replacement level).

[17] Bottles of HC for stress dosing (see Section 4.1.4.4) will be dispensed starting at Day 1 and thereafter as needed to replace opened bottles. Accountability for bottles of HC will be performed at every study visit.

[18] Subjects will use an electronic study diary to document study drug and background GC adherence. Female subjects will also use the study diary to record menstrual information (including start and stop dates of menses).

[19] A full physical examination will be conducted at Baseline (Day 1), Week 24, 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. (In Italy and Poland, the physical exam will not be performed at the subject's home and must be performed in the clinic).

1.3.5 Schedule of Optional Open-Label Extension Period Activities

	Extension Treatment Period											Follow-up	ET
STUDY VISIT NUMBER	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
STUDY WEEK	**88**	**100**	**124**	**148**	**172**	**196**	**220**	**244**	**268**	**292**	**316**	**320**	
STUDY DAY[1]	**617**	**701**	**869**	**1037**	**1205**	**1373**	**1541**	**1709**	**1877**	**2046**	**2213**	**Last dose +30 days**	
Study Visit (V)	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**
Urine pregnancy test for FCP	X	X	X	X	X	X	X	X	X	X	X	X	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[5]			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]
DXA scan for body composition and bone mineral density[7]			X		X		X		X		X		X
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[8]	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[9]	X	X	X	X	X	X	X	X	X	X			
Dispense HC for stress dosing and perform accountability[10]	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; DXA; dual-energy x-ray absorptiometry (scan); ET, early termination; FCP, female of childbearing potential; GC, glucocorticoid; HC(e), hydrocortisone (equivalents); SF-36, Short Form 36; V, study visit

[1] For subjects who continue to the optional Open-Label Extension Period, Week 76 visit (as reflected in Table 1.3.4) will be considered as Study Visit 1 for the optional Open-Label Extension Period and will be performed within ±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 (± 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] DXA scans should be performed for all subjects as indicated. Subjects should not take calcium supplements within the 24 hours before a DXA scan.

[8] Either the subject will pick up study drug in the clinic or the clinic will ship 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. (In Denmark, UK, Ireland, Romania, Estonia or Turkey shipping of study drug directly from clinic to subject's home is not permitted.)

[9] 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 no more than 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).

[10] Bottles of HC for stress dosing (see Section 4.1.4.4) 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 CRF_1 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.

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 CAH, a goal of chronic GC replacement therapy is to administer a GC dose that suppresses adrenal androgen overproduction due to ACTH stimulation. Serum A4 is a biochemical marker of adrenal androgen production. A goal of GC therapy is to suppress adrenal androgen production to a level that is at or slightly above the age and sex adjusted normal range (eg, A4 >ULN but <1.25x ULN). An A4 level substantially above the age and sex adjusted ULN is

consistent with the GC dose being insufficient to appropriately suppress ACTH-driven adrenal androgen production. An A4 level substantially below the age and sex adjusted ULN is consistent with over-suppression of ACTH-driven adrenal androgen production due to too high of a GC dose.

By modulating ACTH release, it is postulated that tildacerfont will allow a lower daily GC replacement dose, while maintaining control of adrenal androgen production. To evaluate this hypothesis, A4 levels will be used to monitor the impact of glucocorticoid replacement therapy on adrenal androgen production.

SPR001-204 is a randomized, double-blind, placebo-controlled study that will evaluate the potential of tildacerfont to reduce GC burden in adult subjects with classic CAH who have LLD ≤ A4 ≤ 2.5x ULN and are on supraphysiologic doses of GC therapy (≥30 mg/day and ≤60 mg/day HCe). SPR001-204 will be the first study of tildacerfont to evaluate GC dose reduction. In addition, Study SPR001-204 will characterize clinical outcomes after up to 76 weeks of treatment with tildacerfont. An optional Open-Label Extension Period will provide an 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/m^2 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 CRF_1 receptors on the pituitary gland. In vitro studies show that tildacerfont binds to CRF_1 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 CRF_1 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 CRF_1 receptor antagonist that is highly selective for the human CRF_1

over the human CRF_2 receptor (6.1 nM vs >100 nM, respectively) and inhibits CRF-stimulated human CRF_1 receptor function.

Nonclinical safety pharmacology studies have indicated no undesirable pharmacodynamic (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 6.5.1 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/aneugenic.
- 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 ≤1000 mg/kg/day. In rabbits, maternal toxicity was observed at ≥30 mg/kg/day, and embryo-fetal developmental toxicity was observed at ≥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 CRF_1 receptor antagonist in CAH patients was demonstrated in the Phase 2 Study SPR001-201, which showed clinical evidence of CRF_1

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 [~39-fold higher exposure in rat than the expected average exposure for the human dose in this study] for 26 weeks)
- Hepatocellular hypertrophy (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 exposure in dog than the expected average exposure for the 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 for the human dose in this study] for 26 weeks) or of CYP1A1, CYP2B11, and CYP3A12 (in dogs dosed with ≤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 for the 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 for the 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 than the expected average exposure for the 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 CRF_1 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 CRF_1 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 tildacerfont 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 total daily dose of 200 mg, 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 CRF_1 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 investigation of tildacerfont's potential to reduce GC use and of extended treatment with tildacerfont for up to 76 weeks in subjects with CAH. An optional Open-Label Extension Period will provide an 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 mean absolute GC change in subjects with classic CAH over the 24 -week, Double Blind, Placebo-Controlled Treatment Period	Absolute change from baseline in GC dose in HCe at Week 24
Secondary Efficacy	
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels while maintaining androgen control in subjects with CAH	Proportion of subjects with GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or A4 ≤ ULN at Week 24
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels while maintaining androgen control in subjects with CAH	Proportion of subjects with baseline GC dose ≤ 35mg HCe who achieve GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or ≤ ULN at Week 24
To evaluate the effect of tildacerfont in reducing cardiovascular risk in subjects with CAH	Proportion of subjects with improvement in at least one cardiovascular risk factor at Week 24
Exploratory Efficacy	
To evaluate the percentage change in GC use in subjects with CAH	Percent change from baseline in GC dose at Week 24
To evaluate the effect of tildacerfont in reducing the cumulative HCe dose in subjects with CAH	Change in total cumulative GC dose in HCe at Week 24
To evaluate the effect of tildacerfont in improving HOMA-IR in subjects with CAH	Change from baseline in the HOMA-IR at Week 24
To evaluate the effect of tildacerfont in improving HOMA-IR after 52 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in HOMA-IR after 52 weeks of tildacerfont treatment

Objectives	Endpoints
To evaluate the effect of tildacerfont in reducing cardiovascular risk in subjects with CAH	Proportion of subjects with improvement in at least one cardiovascular risk factor at Week 52
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels while maintaining androgen control in subjects with CAH	Proportion of subjects with GC dose ≤ 11 mg/m2/day and A4 ≤ 1.2x baseline or ≤ ULN at Week 52
To evaluate the effect of tildacerfont in improving QoL in subjects with CAH	Change from baseline at Week 24 in the SF-36 total score
To evaluate the effect of tildacerfont in improving quality of life in subjects with CAH	Change from baseline at Week 52 in the SF-36 total score
To evaluate the effect of tildacerfont on BMI after 24 weeks in subjects with CAH	Percent change from baseline in BMI at Week 24
To evaluate the effect of tildacerfont on BMI after 52 weeks of tildacerfont treatment in subjects with CAH	Percent change from baseline in BMI after 52 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont on wc after 52 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in wc after 24 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont on waist circumference after 52 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in waist circumference after 52 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont in improving body composition after 52 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in fat mass and fat/lean mass percentage ratio after 24 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont in improving body composition after 52 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in fat mass and fat/lean mass percentage ratio after 52 weeks of tildacerfont treatment
To evaluate the effect of tildacerfont in improving BMD after 52 weeks of tildacerfont treatment in subjects with CAH	Change from baseline in BMD after 52 weeks of tildacerfont treatment

Objectives	Endpoints
To evaluate the effect of tildacerfont in reducing TART(s) in male CAH subjects with TART(s) at baseline after 24 weeks of tildacerfont treatment in subjects with CAH	Proportion of male subjects with reduction in TART volume at Week 24 who had TART(s) at baseline
To evaluate the effect of tildacerfont in reducing TART(s) in male CAH subjects with TART(s) at baseline after 52 weeks of tildacerfont treatment in subjects with CAH	Proportion of male subjects with reduction in TART volume at Week 52 who had TART(s) at baseline
To evaluate the effect of tildacerfont in reducing GC use while maintaining normal A4 levels at Week 24 in subjects with CAH	Proportion of subjects with at least a 5 mg/day HCe reduction from baseline (Day 1) in GC dose and A4 ≤ 1.2x baseline or ≤ ULN at week 24
To evaluate the effect of tildacerfont in reducing GC use while maintaining normal A4 levels at 52 weeks in subjects with CAH	Proportion of subjects with at least a 5 mg/day HCe reduction from baseline (Day 1) in GC dose and A4 ≤ 1.2x baseline o ≤ ULN at week 52
Exploratory Efficacy (Optional Open-Label Extension Period)	
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels in subjects with CAH	Proportion of subjects with GC dose ≤11 mg/m2/day in HCe and A4 ≤ULN at 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 improving BMD in subjects with CAH	Change from baseline in BMD 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 2-part treatment period that will evaluate the potential of tildacerfont to reduce GC burden in adult subjects with classic CAH who have LLD ≤ A4 ≤ 2.5x ULN and are on supraphysiologic doses of GC therapy (≥30 mg/day and ≤60 mg/day in HCe). The first 24 weeks of the treatment period will be a randomized, double-blind, placebo-controlled study in which subjects are randomized in a 1:1 ratio to receive either placebo or tildacerfont at 200 mg QD. All subjects will receive open-label tildacerfont at 200 mg QD during the remaining 52 weeks of the treatment period. An optional Open-Label Extension Period will provide an open-label treatment with tildacerfont at 200 mg QD for up to 240 weeks.

Refer to the study schematic provided in Section 1.2.

4.1.1 Study Periods

This study will consist of the following periods:

- A ≤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 SPR001-203 to this study) will be used to determine eligibility and fulfill screening requirements for this study.

In Germany, screening information from Spruce Biosciences Study SPR001-203 is not permitted to be transferred to determine study eligibility.

A 6- or 12-week *Glucocorticoid Conversion Period* (Week -12 to either Week -6 or Week -2 [±3 days]) for subjects on dexamethasone at the initial Screening Visit who agree to convert to a non-dexamethasone regimen as determined by their physician (Section 1.3.3)

- A 76-week, 2-part *Treatment Period*
  - The 24-week *Placebo-Controlled Treatment Period* (Day 1 to Week 24) will be randomized, double-blind, and placebo-controlled. Subjects will be randomized in a 1:1 ratio to receive either placebo or tildacerfont at 200 mg QD.
  - The 52-week *Open-Label Period* (day after Week 24 to Week 76) will provide subjects who complete the Placebo-Controlled Treatment Period with 52 weeks of open-label treatment with tildacerfont 200 mg QD.
  - Beginning at Week 2 (based on the Day 1 A4 measurement), subjects with an A4 measurement ≤ ULN at a study visit will begin to reduce their daily GC dose by increments of no more than 5 mg/day HCe each time, down to a minimum of 15 mg HCe per day. Beginning at Week 6 (based on Week 6 A4 measurement), subjects with an A4 >1.25x ULN will begin to increase their daily GC dose by increments of no more

than 5 mg/day HCe each time. More details on GC dose adjustments are provided in Section 4.1.4.3.

- Subsequent GC dose adjustments are based on A4 measurements at Weeks 12, 18, 24, 32, 40, 52 and 64.

- 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 4.1.4.3).
- A 30-day *Follow-up Period at EOT*
  - Subjects who do not continue to the Open-Label Extension Period upon completion of Treatment Period 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.

4.1.2 Study Visits and Telephone Contacts

4.1.2.1 Study Visit Schedule

- During the Screening Period:
  - Optional A4 Screening Visit
  - Screening Visit at ≤45 days before Day 1
- During the Glucocorticoid Conversion Period (for subjects on dexamethasone at Screening): visits at Weeks -12 and -8 (and -2, if applicable); scheduled telephone contacts at Weeks -11 and -6 (and -5, if applicable)
- During the 24-week Placebo-Controlled Treatment Period: visits on Day 1 (baseline) and at Weeks 3, 6, 12, 18, and 24
- During the 52-week Open-Label Period: visits at Weeks 32, 40, 52, 64, and 76; scheduled telephone contacts at Weeks 27 and 46
- 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 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.

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.

For post-Screening activities, the investigational site will decide how to conduct these activities if alternatives are necessary due to COVID-19 restrictions, taking into consideration subject preference and the relevant local public health guidelines and striving to maintain a consistent mode for each activity throughout the study. 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), 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 during the Glucocorticoid Conversion Period at Weeks -11 and -6 (and -5, if applicable) and during the Treatment Period at Weeks 27 and 46 to record any AEs and concomitant medications.

After receiving A4 results from the Day 1 (dose reduction only) and Week 6, 12, 18, 24, 32, 40, 52, and 64 study visits, or during the optional Open-Label Extension Period, sites will make telephone contacts to subjects who are eligible for a GC dose adjustment. Sites will contact these subjects within 2 weeks after each applicable study visit. 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 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 GC 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

During the Glucocorticoid Conversion and Treatment Periods, subjects will use an electronic study diary to document study drug and background GC adherence. Female subjects will also use the study diary to record menstrual information (including start and stop dates of menses).

4.1.4 Procedures for Glucocorticoids

4.1.4.1 General Procedures for Glucocorticoids

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 that particular GC regimen, and any GC stress dosing during the past year.

To be eligible to enter this study, subjects must be on a stable dose of GC replacement ≥30 mg/day and ≤60 mg/day in HCe for ≥1 month before screening without any evidence of non-adherence to the GC regimen during this period (stress dosing is allowed). For any subject whose prescribed total daily GC dose varies from day to day but is stable on a weekly basis, an average total daily dose based on the total weekly dose will be calculated to determine eligibility.

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 the study could necessitate an adjustment to the subject's mineralocorticoid regimen. The adequacy of a subject's mineralocorticoid dose should be monitored throughout the study and adjusted as needed to adequately maintain standing blood pressure, plasma renin levels, and electrolytes (serum potassium in particular) within acceptable ranges (Speiser 2018).

Please see instructions for administration of GCs through Week 24 and after Week 24 below.

Administration of GCs through Week 24:

- Participants who enter the study under protocol versions prior to Protocol Version 7.0 will receive Sponsor-supplied GCs
- Participants who enter the study under Protocol Version 7.0 and higher will receive Principal Investigator-prescribed GCs*
- Participants should remain on the same GC (not the same dose) through week 24. If a change is necessary due to drug shortage, etc., switching within the same type of GC (i.e., intermediate – intermediate/prednisone – prednisolone) is allowed. Any such changes should be discussed with the Medical Monitor.

  *In countries where prednisolone 1mg is not commercially available, the Sponsor will provide this GC through week 24

Administration of GCs after Week 24:

- Participants who enter the study under any protocol version (1 and higher) will use Principal Investigator-prescribed GCs
- A change in GC type (e.g., prednisone to prednisolone) is acceptable after Week 24 (see note on change between types of GC below)

Subjects should not switch between short-acting and intermediate-acting GCs because it could confound interpretation of morning biomarker levels (e.g., if a subject switches from HC to prednisolone and the morning A4 decreases, it may be difficult to ascertain if the A4 decrease is due to longer GC coverage overnight or study drug effect). Half-lives of intermediate-acting GCs are similar enough that confounding interpretation should not be a concern when switching

from one intermediate-acting GC to another. For example, after Week 24, subjects could switch between prednisone to prednisolone (one intermediate-acting GC for another) but should not switch between short-acting and intermediate-acting GCs unless necessary based on GC availability. Any such cases should be discussed with the Medical Monitor.

Sponsor acknowledges that the protocol uses a 1:4 ratio for HC: prednisone and 1:5 for HC: prednisolone. 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.

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 times. Mineralocorticoid may be taken at any time of day, but its timing relative to laboratory assessments should be consistent throughout the study.

4.1.4.2 Glucocorticoid Dose Conversion to Hydrocortisone Equivalents

Table 1 defines the potencies of various GCs relative to HC in treating CAH in HCe. The table provides the conversion units for subjects who are converting from dexamethasone to another GC and provides the units to convert GC mg to HCe units to conduct GC dose changes.

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. Glucocorticoid Dose Conversion to Hydrocortisone Equivalents (HCe)

Glucocorticoid	Potency in CAH (HCe)
Hydrocortisone	1
Prednisone	4[1]
Prednisolone or methylprednisolone	5[1,2]
Dexamethasone	60 to 80[3]

[1] Zoorab 1998. [2] Clayton 2002. [3] Rivkees 2010; Speiser 2018. The Investigator may use a conversion factor for dexamethasone in the range specified, based on clinical judgment. 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.

4.1.4.3 A4-Based Daily Glucocorticoid Dose Adjustment Algorithm

Any adjustment of GC dose will be based on the A4 level measured at study visits and made in increments ≤5 mg/day HCe according to the standardized sets of GC regimens (Table 1).

The below A4-based algorithm will be used to guide changes to GC replacement therapy. Reductions below 15 mg/day should be discussed with the Medical Monitor.

A4 Level ≤ULN

- Reduce GC dose
- GC dose reductions may begin on Week 2 (based on Day 1 measurement) and thereafter at Week 6, 12, 18, 24, 32, 40, 52, and 64 study visits, or during the optional Open-Label Extension Period

A4 Level >1.25x ULN

- Increase GC dose
- GC dose increases can occur at Week 6, 12, 18, 24, 32, 40, 52, and 64 study visits, or during the optional Open-Label Extension Period

A4 level >ULN and ≤1.25x ULN

- Maintain GC Dose

The Investigator should contact the Medical Monitor if the Investigator does not intend to follow A4-based GC dose adjustment algorithm at a visit.

The daily GC dosing frequency (e.g., BID or 3 times daily [TID]) should remain stable throughout the study. The Investigator should contact the Medical Monitor if the Investigator intends a change to the GC dosing frequency at a visit.

If a change in GC is warranted by the A4 algorithm, sites will contact subjects by telephone within 2 weeks after each applicable study visit. If no GC dose adjustment is warranted based on the A4 level, the site does not need to contact the subject.

Sites will telephone subjects again 7 days after GC dose adjustment to assess for the occurrence of AEs and the initiation of new concomitant medications.

4.1.4.4 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 specified 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. Daily replacement dosing from the subject's or Sponsor-provided 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)	• 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)[1] • Increase 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	• HC 100 mg IM or SC
Minor to moderate surgical stress	• HC 25 to 75 mg/24 hours (usually 1 to 2 days)
Major surgery with general anesthesia, trauma, or disease that requires intensive care	• 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% NaCl • Rapid tapering and switch to oral regimen depending on clinical state
Acute adrenal crisis	• 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 day • Rapid 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 needs • For 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/min • Cardiac 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.

[1] When 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, generally 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.

4.1.4.5 Post-Treatment Glucocorticoid Dosing

Upon completion of the Treatment Period, 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.

4.2 Scientific Rationale for Study Design

In previous Phase 2 open-label 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. Study SPR001-204, which has a 24-week randomized, double-blind, Placebo-Controlled Treatment Period followed by a 52-week Open-Label period and will enroll approximately 90 subjects, will provide a more definitive, longer-duration, powered dataset. An optional Open-Label Extension Period will provide up to an additional 240 weeks of open-label treatment with tildacerfont at 200 mg QD. The placebo treatment group will control for any potential placebo effects in CAH and their impact on the overall tildacerfont treatment effect.

Given the problematic nature and significant side effects of standard-of-care CAH therapy using chronic supraphysiologic GC replacement (see Section 2.2.2), an important goal of treatment in CAH is the reduction of GC dose requirements (Speiser 2018). To that end, Study SPR001-204 will be the first clinical study to evaluate the potential GC-sparing effects of tildacerfont in subjects with CAH, with change in GC dose after 24 weeks of study drug as its primary endpoint and other measures of GC dose reduction as secondary endpoints. To evaluate tildacerfont's potential to reduce GC use in CAH, Study SPR001-204 will enroll subjects who are taking supraphysiologic doses of GCs (and have LLD ≤ A4 ≤ 2.5x ULN) and gradually reduce the GC regimen in subjects who maintain A4 ≤ULN during the Treatment Period.

Study SPR001-204 will enroll subjects who are taking supraphysiologic doses of GCs and have LLD ≤ A4 ≤ 2.5x ULN. Based on subgroup analyses of data from previous Phase 2 studies, these subjects constitute an appropriate subpopulation of CAH patients for evaluating reductions in GC dose. Eligibility for the previous Phase 2 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 in these studies. When baseline A4 and ACTH levels were instead used to stratify subjects into subgroups, 2 distinct subgroups were revealed 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 and would require reduction of key hormones before any GC dose reduction. In contrast, the subgroup of subjects with lower A4 and ACTH were on a higher mean GC dose and constitute an appropriate subpopulation of CAH patients for a study of GC reduction. Enrolling this subpopulation of CAH patients will provide a more homogeneous study population from which to draw more robust conclusions.

Study SPR001-204 will treat subjects with tildacerfont for up to 76 weeks, significantly longer than previous Phase 2 studies. The initial Phase 2 Study SPR001-201 treated subjects with tildacerfont for 2 weeks at each dose level ranging from 200 mg to 1000 mg per day. The subsequent Phase 2 Study SPR001-202 treated subjects with tildacerfont for 12 weeks at 400 mg QD. 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. Study SPR001-204 will treat subjects with randomized study drug for 24 weeks during the Placebo-Controlled Treatment Period and with open-label tildacerfont for a further 52 weeks during the Open-Label Period. An optional Open-Label Extension Period will provide up to an additional 240 weeks of open-label treatment with tildacerfont at 200 mg QD. This duration of treatment will provide much longer-term monitoring of clinical outcomes for this chronic drug. 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.

Subjects cannot be on dexamethasone during this study because dexamethasone may have a moderate drug interaction with tildacerfont that would confound efficacy analysis. Based on nonclinical and Phase 1 clinical data, tildacerfont is a moderate inhibitor of CYP3A4. Dexamethasone is primarily metabolized through CYP3A4, and GC exposure data from Study SPR001-201 have shown a potential for drug-drug interaction (DDI) 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. In contrast, 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 DDI (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.

In CAH, a goal of chronic GC replacement therapy is to administer a GC dose that suppresses adrenal androgen overproduction due to ACTH stimulation. Serum A4 is a biochemical marker of adrenal androgen production. A goal of GC therapy is to suppress adrenal androgen production to a level that is at or slightly above the age and sex adjusted normal range (eg, A4 >ULN but <1.25x ULN). An A4 level substantially above the age and sex adjusted ULN is consistent with the GC dose being insufficient to appropriately suppress ACTH-driven adrenal androgen production. An A4 level substantially below the age and sex adjusted ULN is consistent with over-suppression of ACTH-driven adrenal androgen production due to too high of a GC dose.

By modulating ACTH release, it is postulated that tildacerfont will allow a lower daily GC replacement dose, while maintaining control of adrenal androgen production. To test this

hypothesis, A4 levels will be used to monitor the impact of GC replacement therapy on adrenal androgen production.

Another important goal of treatment in CAH is the reduction of adrenal hormone levels. To that end, this study will also measure the effect of tildacerfont on key hormones (ACTH, A4, 17-OHP). Other exploratory efficacy endpoints will assess additional clinical benefit associated with reduction in GC dose and hormone control, such as improvements to QoL, metabolic parameters, and BMD.

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 SPR001-204, tildacerfont tablets will be administered at 200 mg QD for up to 76 weeks. Data from previous Phase 1 and Phase 2 studies support the safety and potential PD effects of this dose.

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 ≤200 mg/day has been well tolerated in previous clinical studies.

The clinical efficacy/PD data show CRF_1 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).

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 that a dose of ≤200 mg/day tildacerfont may provide maximum benefit while minimizing drug exposure.

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 a tildacerfont tablet dose of 200 mg QD for testing in Study SPR001-204. This dose lies within a clinically precedented dose range that has both been well tolerated and produced responses in key hormones.

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 76 weeks of the Treatment Period. A subject is considered to have completed the study if the subject has completed study treatment and the last 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 90 subjects with classic CAH currently receiving GC at a supraphysiologic dose (defined in Section 5.1.1). 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 SPR001-203 to this study 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.

In Germany, screening information from Spruce Biosciences Study SPR001-203 is not permitted to be transferred to determine study eligibility.

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, dexamethasone (or a combination of the aforementioned GCs)

3. Has LLD ≤ A4 ≤ 2.5x ULN at screening measured before an AM GC dose
4. Has been on a stable, supraphysiologic dose of GC replacement (defined as ≥30 mg/day and ≤60 mg/day in HCe) for ≥1 month before screening
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 CRF_1 receptor antagonist
4. Shows clinical signs or symptoms of adrenal insufficiency
5. 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 m^2
    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
6. 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 baseline (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 baseline
7. 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
8. Routinely works overnight shifts
9. 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
10. Females who are pregnant or nursing
11. Use of any other investigational drug from 30 days or 5 half-lives (whichever is longer) before screening to the end of the study
12. Use of the following drugs from 30 days or 5 half-lives (whichever is longer) before the start of the Treatment Period 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 μg 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)
13. 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.

Subjects should not take calcium supplements within the 24 hours before a dual-energy X-ray absorptiometry (DXA) scan.

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 μg 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.

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 hormone inclusion criteria may be rescreened if their GC dose is adjusted 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 Day 1 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 SPR001-203 to this study may be used to determine eligibility and fulfill screening requirements for this study.

In Germany, screening information from Spruce Biosciences Study SPR001-203 is not permitted to be transferred to determine study eligibility.

6 STUDY INTERVENTION

6.1 Study Intervention Administration

6.1.1 Study Intervention Description

Tildacerfont is a small-molecule CRF_1 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, GC regimens, or HC for stress dosing provided by the Sponsor.

6.1.2 Treatment Assignment, Dosing, and Administration

At the beginning of the Placebo-Controlled Treatment Period, subjects will be randomized in a 1:1 ratio to receive either placebo or tildacerfont at 200 mg QD for 24 weeks. During the Open-Label Period, all subjects will receive open-label tildacerfont at 200 mg QD for 52 weeks. During the optional Open-Label Extension Period, subjects will continue to receive tildacerfont at 200 mg QD.

Study drug will be taken 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.

Subjects entering the study under protocol version 7.0 will use a Principal Investigator-prescribed supply of GCs. Subjects who entered the study under prior protocol versions will continue to use the GCs provided by the Sponsor through Week 24. After Week 24, subjects will use a Principal Investigator-prescribed supply of GCs. Subjects will continue to use the same type of GC (example: switch between short-acting GC and intermediate acting GC shall not be allowed) throughout the study. Please see important details on GC use in Section 4.1.4.1.

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 times. Mineralocorticoid may be taken at any time of day, but its timing relative to laboratory assessments should be consistent throughout the study.

Only authorized study staff may dispense study treatment. 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.

In Denmark, UK, Ireland, Romania, Estonia or Turkey shipping of study drug directly from clinic to subject's home is not permitted

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 drug and study GC 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 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 the drug product but contain no drug substance.

Study drug tablets will be supplied in blister cards.

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

In the United States, a 50mg and/or 200 mg of drug substance tablet will be available. The tablets may be packaged into HDPE bottles for use in the open label extension portion of the study.

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

At the beginning of the Placebo-Controlled Treatment Period, subjects will be centrally randomized in a 1:1 ratio to receive placebo or tildacerfont at 200 mg QD using a randomization and trial supply management (RTSM) system. Randomization will be stratified by sex and baseline GC dose level (<40 mg/day and ≥40 mg/day in HCe).

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 (see Section 4.1.3). Subjects will return study treatment at each study visit for a pill count. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol.

Compliance information to be reviewed will include (but not be limited to) adherence to the subject's GC regimen (including consistency in timing of doses), 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 (Section 6.5.1) and the list of other medications of concern (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.

Information on concomitant GC therapy is presented in Section 4.1.4.

6.5.1 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.

6.5.1.1 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 rationale in Section 4.2). 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.

6.5.1.2 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 μg, 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 μg 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. 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 Treatment Period and Follow-up Activities) on subjects who discontinue study drug.

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.

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 Treatment Period and Follow-up 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		Action
ALT ≥5x ULN		Discontinue study drug and notify Sponsor
ALT ≥3x ULN	**AND** total bilirubin ≥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 ≥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 ≥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 ≥3x ULN and bilirubin ≥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 baseline 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 (e.g., 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 baseline 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 adverse events of adrenal insufficiency.

If the Investigator deems the sign(s), symptom(s) and/or laboratory finding(s) to be due to adrenal insufficiency, the adverse event 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 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 SAE definition (Section 8.3.2) or the definition of an adrenal crisis (Section 4.1.4.4, 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.

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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 Treatment Period and Follow-up 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 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), all described in this section. Quality of life as reflected by mood will be measured using the HADS, which is also used as a measure of safety and is described in Section 8.2.6.2.

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). HOMA-IR will be calculated from fasting glucose and fasting insulin. Blood pressure (systolic and diastolic) will be assessed. Body weight, BMI, and wc will be assessed as described in Section 8.2.3.

DXA is a whole-body scan that measures both total body composition (including the mass of fat, bones, and lean tissue) and BMD. One whole-body DXA scan exposes an individual to an effective radiation dose of <10 microSieverts, comparable to the normal background radiation of 1 day at sea level (Shepherd 2017). DXA scans should be performed for all subjects according to the Schedule of Treatment Period and Follow-up Activities. However, DXA scans will be optional at study centers that lack access to a DXA scanner. The initial DXA scan may be scheduled for any time before the first dose of study drug and will be considered the baseline measurement for the BMD endpoint and body composition assessments. Subjects should not take calcium supplements within the 24 hours before a DXA scan.

8.1.4 Bone Biomarker Assessments

Bone-specific alkaline phosphatase (BSAP), procollagen type 1 N terminal propeptide (P1NP), and osteocalcin are markers of bone formation. C-terminal telopeptide of type 1 collagen (CTX-1) and urinary N-linked telopeptide of type 1 collagen (U-NTx) are markers of bone turnover that will be assessed according to the Schedules of Activities.

8.1.5 Hyperandrogenic Symptoms

8.1.5.1 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 before the first dose of study drug and will be considered the baseline measurement for the TART assessment. 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.

8.1.5.2 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 24, and Week 76. If the physical exam is performed at the subject's home, the qualified medical professional will conduct a full physical exam and report any changes to the subject's health to the site to determine whether further evaluation is needed via an unscheduled visit.

In Germany, only post-screening physical exams are eligible to be conducted at the subject's home.
In Italy and Poland, home visits are not permitted, and physical examinations must occur in the clinic.

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, Fat Mass, and Waist Circumference

Body weight will be measured at every visit using a calibrated balance. The balance 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.

Fat mass will be assessed by DXA.

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 baseline and Weeks 12, 24, 52, 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 or study GC. 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 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, 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 (e.g., 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 (e.g., for workup of persistent pre-treatment lab abnormality)
- Social admission (e.g., subject has no place to sleep)
- Administrative admission (e.g., for yearly physical exam)
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., 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 or Study Glucocorticoid (Study Treatment)

The Investigator will assess the relationship of each AE separately to study drug and to the study GC according to the categories in Table 5. This assessment will serve to determine whether there exists a reasonable possibility that the study drug or study GC caused or contributed to the AE.

Table 5. Relatedness of Adverse Event to Study Drug or Study Glucocorticoid

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY RELATED: This category applies to those AEs that are judged to be unrelated to study treatment but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study treatment if or when it meets two of the following criteria: (1) it does not follow a reasonable temporal sequence in relation to administration of study treatment; (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 study treatment; or (4) it does not reappear or worsen when study treatment is re-administered.
POSSIBLY RELATED: This category applies to those AEs for which a connection to study treatment administration cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets two of the following criteria: (1) it follows a reasonable temporal sequence in relation to administration of study treatment; (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 study treatment.
PROBABLY RELATED: This category applies to those AEs that the Investigator thinks are related to study treatment with a high degree of certainty. An AE may be considered probably related if or when it meets three of the following criteria: (1) it follows a reasonable temporal sequence in relation to administration of study treatment; (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 treatment. There are exceptions when an AE does not disappear upon discontinuation of study treatment yet treatment-relatedness clearly exists (e.g., as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to study treatment.
DEFINITELY RELATED: This category applies to those AEs that the Investigator thinks are incontrovertibly related to study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence in relation to administration of study treatment; (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 treatment and recurs with re-exposure to study treatment (if rechallenge occurs); and (4) it follows a known pattern of response to study treatment.

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 study GC administration will be considered and investigated.

AEs classified as unrelated or unlikely related to study treatment will be considered not related to treatment, and AEs classified as possibly, probably, or definitely related to study treatment 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 should be recorded but will not be considered TEAEs. If the AE occurs on the date of the first dose of study drug, 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 treatment, 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 definition (e.g., 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 (e.g., 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 a patient diary during episodes of GC stress dosing: start and stop date, concomitant medications, cause for stress dosing (e.g., infection, strenuous exercise, emotional stress, pain, surgery) and concurrent AEs. Adverse events resulting in 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 (± 1 hour) for measurement of tildacerfont concentration at each study visit indicated in the Schedule of Treatment Period and Follow-up 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

Efficacy endpoints at Week 24 will be evaluated using the following hypothesis-testing schema: The tildacerfont treatment group will be compared with the placebo treatment group. The null hypothesis is that there is no difference in the mean change from baseline to Week 24 in GC dose in HCe. The alternative hypothesis will be that there is a difference between the treatment groups.

Efficacy endpoints after 52 weeks of tildacerfont treatment will be evaluated using the following hypothesis-testing schema: The Week 52 value will be compared with the baseline value. The null hypothesis will be that there is no difference between the Week 52 and baseline values. The alternative hypothesis will be that there is a difference.

9.2 Sample Size Determination

A sample size of N=45 subjects per group will provide at least 90% power to detect a between group difference in the proportion of subjects with at least a 5 mg/day HCe reduction from baseline in GC dose at Week 24 with A4 ≤ULN of at least 33%, assuming the placebo group has a response of 30% and the two-sided type I error is 0.05.

9.3 Populations for Analyses

The ITT Population will include all randomized subjects. The ITT Population will be the primary analysis set for analyzing demographics, baseline characteristics, and efficacy.

The mITT Population will include all randomized subjects who receive at least 1 dose of study drug (tildacerfont or placebo).

The PP Population will include all randomized subjects who have no major protocol deviations that would affect the analysis of efficacy data, defined as the following:

- Subject did not meet efficacy-based inclusion criteria (hormone levels, GC regimen)
- Subject met efficacy-based exclusion criteria (inadequate adherence to GC regimen, night-shift worker)
- Subject's adherence to study drug or the subject-specific GC regimen was <80% over the Treatment Period

Additional criteria may be specified in the SAP. The PP Population will be identified prior to database lock.

The mITT and/or PP Populations may be used for secondary analyses of the primary and secondary efficacy endpoints.

The Safety Population will include all subjects who receive at least 1 dose of study drug (tildacerfont or placebo), 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 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).

Unless otherwise specified, continuous adrenal biomarkers (A4, 17-OHP, ACTH) will be summarized using a 11-point descriptive statistics (i.e., n, mean, standard deviation [SD], median, 25% quartile [Q1], 75% quartile [Q3], minimum, maximum, geometric mean, geometric coefficient of variance [CV%], 95% confidence interval [CI] for geometric mean [including geometric mean ratio and its 95% CI]). Continuous data aside from (A4, 17-OHP and ACTH) will

be summarized using an 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.

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 using the ITT Population as the primary analysis set and using a 2-sided alpha of 0.05.

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.

Secondary and exploratory analyses that evaluate the change from baseline in all subjects after 52 weeks of tildacerfont treatment will combine the subjects randomized to tildacerfont Day 1 to Week 52 data with subjects randomized to placebo tildacerfont treatment data from Week 24 to Week 76.

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 efficacy endpoint is the absolute change from baseline in GC dose in HCe at Week 24. The null hypothesis is that there is no difference in the mean change from baseline to Week 24 in GC dose in HCe. The alternative hypothesis will be that there is a difference between the treatment groups. The ITT Population will be used for the primary analysis of the primary efficacy endpoint. The analysis of the primary endpoint will be summarized using an exact score test through logistic regression using the randomization strata and treatment group 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.

9.4.3 Analysis of the Secondary Efficacy Endpoints

The analysis population for the Secondary Efficacy Endpoint analyses is the ITT analysis set, including all classic CAH subjects who were randomized into the study.

Table 7. Secondary Efficacy Endpoints

Objectives	Endpoints		Analysis
Secondary Efficacy			
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels while maintaining androgen control in subjects with CAH	2.1	Proportion of subjects with GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or A4 ≤ ULN at Week 24	Primary Analysis
To evaluate the effect of tildacerfont in reducing GC use to near-physiologic levels while maintaining androgen control in subjects with CAH	2.2	Proportion of subjects with baseline GC dose ≤ 35mg HCe who achieve GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or ≤ ULN at Week 24	Primary Analysis
To evaluate the effect of tildacerfont in reducing cardiovascular risk in subjects with CAH	2.3	Proportion of subjects with improvement in at least one cardiovascular risk factor at Week 24	Primary Analysis

For Secondary Efficacy Endpoint 2.1 the null hypothesis is that the difference between randomized treatment groups in the proportion of subjects achieving GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or A4 ≤ ULN at Week 24 is equal to zero. The alternative hypothesis is that the difference is not equal to zero.

For Secondary Efficacy Endpoint 2.2 the null hypothesis is that in the subset of subjects with a baseline GC dose ≤ 35mg the difference between randomized treatment groups in the proportion of subjects achieving GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or A4 ≤ ULN at Week 24 is equal to zero. The alternative hypothesis is that the difference is not equal to zero.

Secondary Efficacy Endpoint 2.3 is the proportion of classic CAH subjects who were randomized into the study who improve at least one baseline CV risk factor at 24 weeks from randomization. This proportion is calculated for each treatment group (e.g., placebo, tildacerfont) as the number of subjects at Week 24 who had at least one CV risk factor at baseline (i.e subjects without any CV risk factors will not be included in the analysis) and no longer meets one or more of the baselines CV risk factors at Week 24, divided by the total number of subjects in the ITT analysis who were randomized to that specific treatment and had at least one CV risk factor at baseline.

Additional details on secondary endpoints and analysis may be specified in the SAP.

9.4.4 Analysis of the Exploratory Efficacy Endpoints

The analysis population for Exploratory Efficacy Endpoint analyses is the ITT analysis set, including all classic CAH subjects who were randomized into the study. Detailed information around the analysis of the exploratory endpoints listed in Section 3 is provided in the Statistical Analysis Plan (SAP) Version 1.0.

9.4.5 Analysis of the Exploratory Efficacy Endpoints in the Optional Extension Period

Analysis of the Exploratory Efficacy Endpoints in the Optional Extension Period is not included in the SAP Version 1.0, as it will be described in a separate SAP not yet developed and, therefore, is not addressed herein.

9.4.6 Analysis Evaluation Periods

The primary evaluation period will evaluate baseline to Week 24 comparing the tildacerfont group to the placebo group. Select endpoints will also be evaluated using the following periods:

- After 52 weeks on tildacerfont treatment (Week 52 for the tildacerfont group and Week 76 for the placebo group compared to baseline)
- After approximately 24 weeks on tildacerfont treatment (Week 24 for the tildacerfont group and Week 52 for the placebo group compared to Week 24 for the placebo group)
- After 76 weeks on tildacerfont treatment (Week 76 for the tildacerfont group compared to baseline)
- From baseline to Week 76
- From baseline to EOT

The baseline for each evaluation period will be defined in the SAP.

9.4.7 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.

9.4.7.1 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.

9.4.7.2 Concomitant Medication Data

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

9.4.7.3 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 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.

9.4.7.4 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 in the SAP.

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

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

9.4.7.5 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 sign 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.

9.4.7.6 ECG 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.

9.4.7.7 Psychiatric Evaluations

C-SSRS and HADS data will be listed.

9.4.8 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.

9.4.9 Subgroup Analyses

The following pre-defined subgroups will be analyzed:

- Baseline GC formulation [HC mono therapy, prednisolone/prednisone/methylprednisolone monotherapy, combination therapy]
- Baseline HCe dose [<40 mg/day, ≥40 mg/day], [<35, ≥35 mg/day]

- Sex [male, female]
- A4 ULN at baseline [≤ULN, >ULN]

The subgroups will be used in supportive analysis of the primary endpoint and secondary endpoints, as applicable. Any additional subgroup analyses will be specified in the SAP.

9.5 Primary and Final Analyses

The primary efficacy analysis is planned after all subjects have completed Week 24, at the end of the double-blind treatment period.

The final analyses will occur after the last subject has completed the follow-up visit after Week 76 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 results from Week 76 up to Week 316/320.

9.6 Multiplicity Control

The primary endpoint (absolute change from baseline in GC dose in HCe at Week 24), secondary endpoints (proportion of subjects with GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or A4 ≤ ULN at Week 24, proportion of subjects with baseline GC dose ≤ 35mg HCe who achieve GC dose ≤11 mg/m2/day in HCe and A4 ≤ 1.2x baseline or ≤ ULN at Week 24, and proportion of subjects with improvement in at least one cardiovascular risk factor at Week 24)

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 business days and have them complete final visit safety assessments (abbreviated early termination visits per sponsor guidance). 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 which 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.

Protocol deviations will be included in the Clinical Study Report.

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 temporarily increase the patient's GC dose to accommodate the additional stress and prevent an adrenal crisis (see Section 4.1.4.4). The Sponsor will provide HC for stress dosing to all subjects during the study, starting at the beginning of the Treatment 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, DXA) 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.

In Italy and Poland, if necessary due to COVID-19 restrictions, clinical labs may be conducted as available at a local laboratory instead of a central laboratory. To ensure the quality of data and protection of subjects, remote source data verification may be used, if necessary due to COVID-19 restrictions. The Sponsor will determine the extent and nature of remote source data verification needed.
In Italy and Poland, study drug may be shipped to subjects if necessary due to COVID-19 restrictions.

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

11.2.1 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 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.

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.

In Germany, the Screening Visit will be performed in the clinic. After the Screening Visit, study visits should continue in-clinic, however in the event of COVID-driven challenges, at-home and telemedicine visits can be used to support patient data collection.
In Italy, Poland, all visits will be performed in the clinic. If necessary due to COVID-19 restrictions, the clinic visits may be conducted remotely (via telemedicine) if approved by the site's IRB/EC.

For post-Screening activities, the investigational site will decide how to conduct these activities if alternatives are necessary due to COVID-19 restrictions, taking into consideration subject preference and the relevant local public health guidelines and striving to maintain a consistent mode for each activity throughout the study. 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), the Investigator or Investigator-delegated study personnel must complete these activities for each visit.

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 6.5.1 for more information on prohibited concomitant medications.

Because of their potential impact on the metabolism of tildacerfont, 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 ≤35 μg, 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 μg 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 mg)	lovastatin	repaglinide	triazolam
buspirone	felodipine	mibefradil	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 contract research organization 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 ≥3x ULN AND total bilirubin ≥2x ULN or INR >1.5):

- Fractionate bilirubin, if total bilirubin is ≥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 ≥3x ULN AND total bilirubin ≥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 ≥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 ≥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 Calcium Sodium BUN Creatinine Total protein	ALP ALT/SGPT AST/SGOT GGT Total and direct bilirubin 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-glutamyltransferase; 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 ≥3x ULN plus total bilirubin ≥2x ULN (>35% direct bilirubin) or ALT ≥3x 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.