A Phase 2 Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of SPR001 (Tildacerfont) in Children Aged 2 to 17 Years with Congenital Adrenal Hyperplasia

US IND Number:	131761
Study Number:	SPR001-205
Document Type:	Clinical study protocol
Protocol Version:	5.0 (supersedes Protocol dated 14 October 2022)
Protocol Date:	30 November 2023
Investigational Medicinal Product:	SPR001 (tildacerfont)
Indication:	Congenital adrenal hyperplasia (CAH)
Sponsor:	Spruce Biosciences, Inc. 611 Gateway Boulevard Suite 740 South San Francisco, CA 94080
Registries:	ClinicalTrials.gov: NCT05128942 EU Clinical Trials Registry: NA

Statement of Confidentiality

SPONSOR APPROVAL PAGE

A Phase 2 Study to Evaluate the Safety, Efficacy, and Pharmacokinetics, of SPR001 (Tildacerfont) in Children Aged 2 to 17 Years with Congenital Adrenal Hyperplasia

Study Number: SPR001-205
Protocol Version: 5.0
Protocol Date: 30 November 2023

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

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Phase 2 Study to Evaluate the Safety, Efficacy, and Pharmacokinetics, of SPR001 (Tildacerfont) in Children Aged 2 to 17 Years with Congenital Adrenal Hyperplasia

Study Number: SPR001-205
Protocol Version: 5.0
Protocol Date: 30 November 2023

- I confirm agreement to conduct the study in compliance with the protocol.
- I confirm that I have read the Investigator's Brochure.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol.

Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Site Name: _____

Principal Investigator Name: _____

_____ _____
Principal Investigator's Signature **Date**

PROTOCOL SYNOPSIS

Sponsor: Spruce Biosciences, Inc.	
Study Title: A Phase 2 Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of SPR001 (Tildacerfont) in Children Aged 2 to 17 Years with Congenital Adrenal Hyperplasia	
Protocol Number: SPR001-205	**Phase:** 2

COHORTS 1- 3 (12-week Treatment)	
Objectives	**Endpoints**
Primary	
To evaluate the safety of tildacerfont in participants with CAH	Adverse events (AEs) and serious adverse events (SAEs)
Secondary	
To determine the efficacy of tildacerfont on disease control or reduction of glucocorticoid (GC) use in participants with classic CAH during 12 weeks of treatment	Proportion of participants who achieve a reduction in androstenedione (A4) or reduction in glucocorticoid (GC) dosing during treatment period
To determine the efficacy of tildacerfont on disease control in participants with classic CAH after 4 or 12 weeks of treatment	Proportion of participants with elevated baseline A4 who achieve a reduction in A4 at Week 4
	Proportion of participants with elevated baseline A4 who achieve A4 normalization at Week 4 or Week 12
To determine the consistency of preliminary tildacerfont pharmacokinetics (PK) in participants with those simulated in a physiologically based PK (PBPK) model	Tildacerfont plasma concentrations will be compared with the current PBPK simulation for consistency
Exploratory	
To explore changes in pharmacodynamic (PD) biomarkers in participants with CAH	Change from baseline in adrenocorticotropic hormone (ACTH), 17hydroxyprogesterone (17-OHP), A4, testosterone, and 11-ketotestoterone (11KT)
COHORTS 4, 5, 6, 7, 8, and 9 (4-week Treatment)	
Objectives	**Endpoints**
Primary	
To evaluate the safety of tildacerfont in participants with CAH	Adverse events (AEs) and serious adverse events (SAEs)
Secondary	
To determine the efficacy of tildacerfont on disease control in participants with classic CAH after 4 weeks of treatment	Proportion of participants who achieve reduction in androstenedione (A4) at Week 4
	Proportion of participants who achieve A4 normalization at Week 4

To determine the consistency of preliminary tildacerfont pharmacokinetics (PK) in participants with those simulated in a physiologically based PK (PBPK) model	Tildacerfont plasma concentrations will be compared with the current PBPK simulation for consistency
Exploratory	
To explore changes in pharmacodynamic (PD) biomarkers in participants with CAH	Change from baseline in adrenocorticotropic hormone (ACTH), 17hydroxyprogesterone (17-OHP), A4, testosterone, and 11-ketotestoterone (11KT)
EXTENSION (Cohorts 1-9)	
Objectives	**Endpoints**
Primary	
To evaluate the safety of tildacerfont in participants with CAH	Adverse events (AEs) and serious adverse events (SAEs)
Secondary	
To determine the efficacy of tildacerfont on reduction of glucocorticoid (GC) use in participants with classic CAH	Proportion of participants who achieve reduction in glucocorticoid (GC) dosing (beyond 12 weeks for Cohorts 1-3 and beyond 4 weeks for Cohorts 4-9)
	Proportion of participants who achieve approximately physiologic GC dosing (≤ 11 $g/m^2/d$)
To determine the efficacy of tildacerfont on disease control in participants with classic CAH	Proportion of participants with elevated A4 at completion of treatment period (Week 12 for Cohorts 1-3 and Week 4 for Cohorts 4-9) who achieve a reduction in A4
	Proportion of participants with elevated A4 at completion of treatment period who achieve A4 normalization
Exploratory	
To explore changes in pharmacodynamic (PD) biomarkers in participants with CAH	Change from baseline in adrenocorticotropic hormone (ACTH), 17hydroxyprogesterone (17-OHP), A4, testosterone, and 11-ketotestoterone (11KT) (at Week 4 for all cohorts and Week 12 for Cohorts1-3)
To explore the impact of tildacerfont on skeletal maturation	Change from baseline in predicted adult height

Study Rationale: Congenital adrenal hyperplasia 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 axis by removing the negative feedback to the hypothalamus and pituitary provided by physiologic cortisol levels. This leads to the compensatory hypersecretion of corticotropin-releasing factor (CRF) by the hypothalamus, overproduction of ACTH by the pituitary gland, and consequent adrenal hyperplasia and overproduction of

downstream adrenal pre-cursors and hormones such as 17-OHP and A4, leading to androgen excess (Merke 2005, Speiser 2018). Androgen excess may result in atypical genitalia in 46,XX newborns, risk for life threatening adrenal crises, ongoing virilization throughout childhood, menstrual dysfunction, early puberty, testicular adrenal rest tumors (TARTs) in males, skeletal maturation leading to compromised adult height, and impaired fertility (Merke and Auchus 2020).

The current standard of care for CAH includes multiple daily doses of oral GCs to replace deficient cortisol. However, as opposed to patients with other forms of adrenal insufficiency, CAH patients generally require supraphysiologic doses of GCs to normalize ACTH and therefore control androgen levels (Claahsen-van der Grinten 2022). This therapy is problematic as it has significant side effects (e.g., loss of bone mineral density, iatrogenic Cushing's syndrome, poor quality of life, metabolic disorders, and increased cardiovascular risk), a narrow therapeutic window, and overall poor treatment effectiveness with higher GC doses conferring increased risk (Stewart 2019). Treatment of children with CAH involves a challenging balance between GC and androgen levels. Elevated androgen levels can cause premature adrenarche and central precocious puberty as well as skeletal maturation leading to compromised adult height. GCs increase metabolic and infection risks and suppress growth by blunting the response to growth hormone (Allen 1998).

Tildacerfont, a potent and highly selective small-molecule antagonist of CRF_1 receptors, is being studied for the treatment of CAH on the basis of its ability to block the CRF_1 receptors in the pituitary gland. This blockage may decrease 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 approximately physiologic replacement levels.

Tildacerfont has been tested in 6 completed Phase 1 studies using single doses ranging from 2 to 800 mg or multiple doses ranging from 50 to 200 mg QD. Once daily dosing has been studied in 2 completed Phase 2 studies using multiple doses ranging from 200 to 1000 mg QD for 2 weeks, and up to 400 mg QD for 12 weeks. Twice daily (BID) dosing of tildacerfont has been well tolerated in adults with CAH in previous clinical studies at doses up to 200 mg BID for 2 weeks. Safety data show that tildacerfont has been generally well tolerated in all clinical studies to date, with no related serious adverse events (SAEs) in current on-going studies.

Data from the 2 completed Phase 2 studies in adults 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) and continued improvement in biomarker levels over a period of 12 weeks.

SPR001-205 will be the first study of tildacerfont in children and will be used to assess safety and to determine the consistency of preliminary tildacerfont PK in pediatrics with those simulated in a PBPK model. It will also characterize changes in androgen levels over the first 4 weeks of treatment (all cohorts), and the ability to reduce GC doses (based on A4 normalization) over 12 weeks of treatment (Cohorts 1-3).

Based on the fact that CYP enzyme activity peaks in early childhood and decreases into adulthood, and CYP3A4 is the primary pathway of tildacerfont elimination, children may have more rapid drug clearance than adults. As a result, BID dosing is being studied to optimize consistency of exposure. All BID dosing regimens have been or will be evaluated in adults prior to being administered to pediatric participants. Thus, two adult cohorts have been added (Cohorts 4 and 5). BID dosing in pediatric participants will be evaluated in Cohorts 6-9.

An optional extension period will provide additional open-label treatment with tildacerfont to provide long-term safety data for up to two years.

Please see Section 1.2 for Study Rationale.

Study Design: This is a Phase 2 open-label study with up to 10 cohorts that will evaluate the safety, efficacy, and PK of different tildacerfont dosing regimens potentially up to 200mg QD for 12 weeks in children with classic CAH, and up to 400mg BID for 4 weeks in children and adults with classic CAH.

Cohorts 1 and 1a (if indicated) and Cohort 2 in children aged 11-17 years and Cohort 3 in children aged 2-10 years will study weight-based dose equivalents of up to 200mg QD, the dose currently being studied in adults with CAH in studies SPR001-203 (12 weeks treatment at 200mg QD) and SPR001-204 (24 weeks treatment at 200mg QD). Treatment in Cohorts 1-3 will be for 12 weeks.

Cohorts 4 and 5 in adults, Cohorts 6 and 8 in children aged 11-17 years, and Cohorts 7 and 9 in children aged 2-10 years will evaluate doses higher than 200mg QD that will be administered BID for 4 weeks.

Cohort 4 (adults) and Cohort 6 (11-17 years) will initiate concurrently at 200mg BID (200 mg BID has been previously evaluated in adults in study SPR001-201). Upon completion of the 4-week dosing on 4 sentinel participants from Cohorts 4 and 6 combined, the DMC will assess safety data and provide recommendations on continued dosing. If the DMC assesses it to be safe to proceed to a higher dose, Cohort 5 (adults) may be initiated at 300mg or 400mg BID and Cohort 7 (2-10 years) may be initiated at 200mg BID. Following the completion of the 4-week dosing periods for Cohorts 5 and 7, the DMC will review safety data from 4 sentinel participants and offer recommendations on whether to proceed to Cohort 8 (11-17 years) and at what dose (300mg or 400mg BID). Following completion of Cohort 8, the DMC will review the safety data from 4 sentinel participants and provide a recommendation on whether to proceed with Cohort 9 and at what dose (300mg or 400mg BID) (Table 1).

All cohorts including doses above 200 mg BID will be adaptive, so that the determination to initiate a cohort, and at what dose, may be determined by the Sponsor, within the guidelines of the protocol, based on recommendations by an independent Data Monitoring Committee (DMC) and emerging safety and exposure data. Individual and study stopping criteria will further ensure safety of the participants.

Please see Section 3 for details on Study Design and Section 6 for details on stopping criteria.

Study Conduct: There are 7 scheduled visits over approximately 18 weeks for Cohorts 1 to 3; and 5 scheduled visits over approximately 10 weeks for Cohorts 4 to 9. Visits are detailed in the Schedule of Activities. All visits should be performed on site, but alternative arrangements may be used if an on-site visit is not feasible. Adverse events and concomitant medications will be collected at each visit.

Any participant enrolled under protocol amendment 3 may be re-consented to protocol amendment 4 and receive the 12-week treatment course; however, because they will have already contributed PK data, they will not be required to have blood draws for tildacerfont concentration on Days 1 and 14 between 0.5 to- 1.5 hours and between 3 to 5 hours post dosing. Additionally, any participant enrolled under amendment 4 (or any other tildacerfont study) may be re-consented and enrolled under protocol amendment 5.

Please see Section 3 and Section 10.2 for details on Study Conduct.

Duration of Participant Participation: Approximately 18 weeks inclusive of Screening, Treatment, and Follow-up for Cohorts 1 to 3; and 10 weeks for Cohorts 4 to 9. The extension period allows for treatment up to 2 years. Please see Section 3.1.2 and Section 3.1.3 for Details on Duration.

Planned Sample Size and Number of Sites: The study is expected to enroll approximately 20 children across the first 3 cohorts (i.e., Cohorts 1, 2, and 3), 10 in the 11-to 17- year age group and 10 in the 2-to 10- year age group. If the optional Cohort 1a is initiated (up to 5 participants), however, Cohorts 1 to 3 may enroll up to 25 children total, 15 in the 11-to 17-year-old age group and 10 in the 2-to 10-year-old age group.

Up to an additional six cohorts (Cohorts 4-9) are planned to investigate BID dosing over 4 weeks of treatment. The study will also enroll up to approximately 15 adults aged ≥18 years across Cohorts 4 and 5; and up to approximately 30 children across 4 additional cohorts [up to 15 in the 11- to 17-year age group (Cohorts 6 and 8) and up to 15 in the 2- to 10-year age group (Cohorts 7 and 9)].

If all possible doses are studied, total sample size of this study may be up to approximately 55 children and 15 adults Please see Table S-1 for subject numbers by dosing cohort:

Table S-1

Cohorts:	Ages (years):	Corresponding Adult Dose	Subject Numbers:
1	11-17	50 mg QD	5
1a	11-17	To be determined based on DMC recommendation (50 or 100 mg QD)	5
2	11-17	200 mg QD	5
3	2-10	50 mg QD, 100 mg QD, OR 200 mg QD	10
4	≥18	200 mg BID	5
5	≥18	300 mg BID and/or 400 mg BID	5+5[1]
6	11-17	200 mg BID	5
7	2-10	200 mg BID	5
8	11-17	300 mg BID and/or 400 mg BID	5+5[1]
9	2-10	300 mg BID and/or 400 mg BID	5+5[1]
			Up to 70 subjects total

[1]+5 allows for the option of dosing 300mg before or after 400 mg Cohort is initiated if indicated by the DMC

The study will be conducted at approximately 15 investigative sites within North America. Please see Section 8.1 for details on Planned Sample size.
Study Drug and Route of Administration: Tildacerfont, an oral small-molecule corticotropin-releasing factor type-1 (CRF_1) receptor antagonist will be supplied as tablets that can be consumed whole or crushed and sprinkled on food. For administration at home, study drug should be taken with food. Study drug may be consumed up to 30 minutes after food, if necessary. If a participant has not consumed study drug within 30 minutes after food, the participant should consume study drug with a snack. Participants will be advised to refrain from consumption of grapefruit, grapefruit juice, or any fruits that are known to be strong CYP3A4 inhibitors (e.g., pomegranate) from 1 day before the first dose of study drug until after the final dose." Please see Section 5 for details on Study Drug.
Participant Population: Patients aged 2 years and older with classic CAH (21-OHD), inclusive of salt-wasting and simple virilizing forms. (Please see Section 1.2.2 for details on Study Population)
Criteria for Inclusion: 1. Male and female participants aged 2 to 10 years (Cohorts 3, 7, and 9), 11 to 17 years (Cohorts 1, 1a, 2, 6, and 8), and ≥18 years (Cohorts 4 and 5) at Screening. 2. For participants aged 2 to 5 years, a minimum weight at Screening of 11 kg. 3. Has a known childhood diagnosis of classic CAH due to 21-hydroxylase deficiency (21-OHD) based on genetic mutation in *CYP21A2* and/or documented (at any time) elevated 17-OHP and currently treated with hydrocortisone (HC), HC acetate, prednisone, prednisolone, methylprednisolone (or a combination of these). Other types of CAH may be allowed with Sponsor approval. 4. For participants in Cohorts 4-9, 1.2X ULN < A4 < 4X ULN. A4 values outside of this range may be allowed with Medical Monitor (MM) approval. 5. A stable dose of GC replacement for ≥1 month before Screening without evidence of non-adherence (as assessed by Investigator). Weight-based dose adjustments or stress dosing in the month prior to Screening are not exclusionary but should be discussed with the Medical Monitor (MM). 6. For participants on mineralocorticoid replacement, a stable dose for ≥1 month prior to Screening. 7. For participants on gonadotropin hormone-releasing hormone (GnRH) analogues, a stable dose initiated ≥ 3 months prior to screening. 8. For participants on aromatase inhibitors, a stable dose for ≥ 3 months prior to screening. 9. If sexually active and capable of reproduction, agrees to follow protocol contraception guidelines. 10. Have provided written informed consent and/or assent, and/or parent/legal guardian permission, as applicable, prior to undergoing any study procedure, including Screening procedures. The participant and/or parent/legal guardian must be able to read and understand all the study procedures. **Criteria for Exclusion:** 1. CAH not due to 21-OHD. 2. History of allergy or hypersensitivity to tildacerfont or other CRF_1 receptor antagonists. 3. History of bilateral adrenalectomy or hypopituitarism. 4. Current treatment with dexamethasone. Participants may be transitioned off dexamethasone prior to Screening at the Investigator's discretion. 5. A clinically significant unstable medical condition, medically significant illness, or chronic disease (other than CAH) within 30 days, including but not limited to:

a. Malignancy or <3 years since remission, except successfully treated localized skin cancer
b. Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 (per the creatinine-based Schwartz equation)
c. Current or history of liver disease (with the exception of Gilbert's syndrome). Resolved/cured viral hepatitis may be allowed with MM approval
d. History of alcohol or substance abuse within the last year, or otherwise that would likely prevent the participant from reliably or safely participating in the study, per Investigator judgement
e. Human immunodeficiency virus (HIV) at Screening
f. Any other condition that would impact participant safety or confound interpretation of study results, in the opinion of the Investigator or MM.

6. Psychiatric conditions, including but not limited to major depression, bipolar disorder, schizophrenia, or schizoaffective disorders that are not effectively controlled on medication and may have an adverse impact on study compliance. Exclusionary symptoms include hallucinations, delusions, and psychosis. Baseline values for depression and anxiety questionnaires are not exclusionary but may inform exclusion of a participant based on Exclusion Criterion 5.
7. Clinically significant abnormal laboratory or electrocardiogram (ECG) results during Screening. Abnormal results requiring review and discussion with the MM to discern eligibility include, but are not limited to:
   a. Any clinically meaningful abnormal ECG results, including Fridericia-corrected QT interval (QTcF) >450 ms (males) or >460 ms (females)
   b. Alanine aminotransferase (ALT) >2x ULN
   c. Total bilirubin >1.5x ULN (except if due to Gilbert's syndrome).
8. Females who are pregnant or nursing.
9. Use of any other investigational drug (other than tildacerfont) or device within 30 days or 5 half-lives (whichever is longer) prior to Screening through the end of the study (EOS). Prior exposure to tildacerfont is allowed, but tildacerfont should be discontinued for at least 2 weeks prior to randomization. The screening window may serve as the washout period.
10. Use of the following drugs from 30 days or 5 half-lives (whichever is longer) before Screening through the EOS:
    a. Rosiglitazone, testosterone, growth hormone, or any other medication or supplement that could impact participant safety or confound interpretation of study results
    b. Moderate to strong inhibitors and/or inducers of cytochrome P450 3A4 (CYP3A4)
    c. Sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 (except hormonal contraception containing $\leq$20 mcg ethinyl estradiol)
    d. 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).
11. Donation or receipt of blood from 90 days before Screening through the EOS; donation or receipt of platelets, white blood cells, or plasma from 30 days before Screening through the EOS.
12. Any known or anticipated swallowing difficulty or dysphagia during Screening or the duration of the study.

Safety Assessments: Safety assessments will include monitoring and recording all AEs (including SAEs, AEs leading to discontinuation/withdrawal, dose-liming toxicities, and AEs of special interest), physical examination, vital signs assessment, ECGs, clinical laboratories, and psychiatric evaluation.

Pharmacodynamic and Tildacerfont Concentration Comparisons:

PD measurements include concentrations of ACTH, 17-OHP, A4, testosterone, and 11KT in the blood. PK measurements will include the plasma concentration of tildacerfont.

For Cohorts 1, 2, 4, 5, 6,7, 8, and 9 (and 1a if indicated), serial blood samples for PK and PD will be drawn during Visits 2 and 3 (Day 1 and Week 2) during the following time windows relative to study drug dosing: pre-dose (pre-GC and pre-tildacerfont dose, approximately 8 AM ± 1 hour), 0.5 to 1.5 hours post-dose, and 3 to 5 hours post-dose. Serial samples should be attempted in all cases but may be declined in the 2–10-year age group at Investigator's discretion (e.g., unable to establish IV, behavioral challenges impede collection and risk other assessments). A blood sample for plasma concentration and PD markers of tildacerfont will be drawn at approximately 8 AM ± 1 hour at all other visits.

For Cohort 3, a blood sample for determining the plasma concentration of tildacerfont and PD markers will be drawn at approximately 8 AM ± 1 hour at all visits. Morning GC and tildacerfont doses must be held until after the blood draw.

Statistical Methods: A sample size of up to 70 participants (i.e., 15 adults, 30 participants 11- to 17-years of age, and 25 participants 2- to 10-years), will provide adequate data to assess the initial safety of tildacerfont in a pediatric and adult population and provide data to support the continued use of the PBPK model to determine pediatric dosing requirements in future studies.

The Safety Population will include all participants who receive at least 1 dose of study drug and will be the primary analysis set for general and safety analyses.

The PK Population will include all participants in the Safety Population with at least 1 post-dose sample above the limit of quantification.

The PD Population will include all participants in the Safety Population with at least 1 evaluable post-baseline PD assessment.

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).

All continuous variables will be presented using an 8-point descriptive summary (n, mean, standard deviation, median, interquartile range [25th percentile, 75th percentile], minimum, and maximum) by dose, as available. Categorical variables will be summarized by frequency and by percentage of participants in corresponding categories.

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

Please see Section 8 for details on Statistical Methods.

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LIST OF ABBREVIATIONS

11KT	11-ketotestosterone
17-OHP	17-hydroxyprogesterone
21-OHD	21-hydroxylase deficiency
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
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BSA	body surface area
CAH	congenital adrenal hyperplasia
CBC	complete blood count
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	corticotropin-releasing factor
CRF_1, CRF_2	corticotropin-releasing factor type-1 or type-2
CRO	contract research organization
C-SSRS	Columbia–Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study

EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
FOCP	female of childbearing potential
GC	glucocorticoid
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GnRH	gonadotropin hormone-releasing hormone
HC	hydrocortisone
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
OTC	over-the-counter
PBPK	physiologically-based pharmacokinetic
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PROMIS	Patient Reported Outcomes Measurement Information System
QD	once daily
QTcF	Fridericia-corrected QT interval
SAE	serious adverse event
SAP	Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
SWYC	Survey of Well-being of Young Children
TART	testicular adrenal rest tumor
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background

1.1.1. Congenital Adrenal Hyperplasia

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 (Merke and Bornstein 2005).

Approximately 95% of patients with CAH have a mutation in the cytochrome P450 21A2 (CYP21A2) gene, which encodes the cytochrome P450c21 enzyme, commonly known as 21-hydroxylase (Anderson 2010, Speiser 2018).

Mutations in other genes that encode enzymes critical in adrenal steroidogenesis (CYP191, 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-hydroxyprogesterone (17-OHP) to 11-deoxycortisol (the precursor to cortisol) (White and Speiser 2000, Bachelot 2008, Doleschall 2014, Auchus 2015). A 21-hydroxylase deficiency (21-OHD) 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. These steroid precursors are then diverted into the synthetic pathway for adrenal androgens, resulting in overproduction of androstenedione (A4) and downstream 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 physiologic cortisol levels. 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 pre-cursors and hormones such as 17-OHP and A4, leading to androgen excess (Merke and Bornstein 2005, Speiser 2018).

The clinical manifestations of CAH are the direct result of cortisol and aldosterone deficiencies and of androgen overproduction (Merke and Bornstein 2005, Anderson 2010, Reisch 2019).

Cortisol deficiency can result in adrenal insufficiency and life-threatening adrenal crises. Androgen excess may result in atypical genitalia in 46,XX newborns, risk for life threatening adrenal crisis, ongoing virilization throughout childhood, menstrual dysfunction, early puberty, testicular adrenal rest tumors (TARTs) in males, skeletal maturation leading to compromised adult height, and impaired fertility (Merke and Auchus 2020).

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 patients with classic CAH 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 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 (caused by impaired cortisol production) in the remaining 25% of classic CAH.

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

1.1.2. Current Treatment for CAH

There are no approved therapies for CAH. The current standard of care for CAH includes multiple daily doses of oral glucocorticoids (GCs) to replace deficient cortisol. However, as opposed to patients with other forms of adrenal insufficiency, CAH patients require supraphysiologic doses of GCs to normalize ACTH and therefore control androgen levels (Claahsen-van der Grinten 2022). This therapy is problematic as it has significant side effects (e.g., loss of bone mineral density, iatrogenic Cushing's syndrome, poor quality of life, metabolic disorders, and increased cardiovascular risk), a narrow therapeutic window, and overall poor treatment effectiveness, with higher GC doses conferring increased risk (Steward 2019). Evidence-based treatment guidelines for CAH are only beginning to be developed (Reisch 2015, Speiser 2018), and current overall treatment effectiveness for patients with CAH is poor (Mnif 2012, Bachelot 2015).

Treatment of children with CAH involves a challenging balance between GC and androgen levels. Elevated androgen levels can cause premature adrenarche and central precocious puberty as well as skeletal maturation leading to compromised adult height. GCs increase metabolic and infection risks and suppress growth by blunting the response to growth hormone (Allen 1998).

Despite the availability of GCs as a treatment for CAH, approximately two-thirds of patients with CAH are considered outside the acceptable bounds of biochemical control based on 17-OHP and A4 levels (Han 2014). Among patients with 21-OHD treated with GCs, normal serum A4 has been shown to be achieved in only 36% of patients (Anderson 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 (Anderson 2010, Auchus 2015).

Given the serious nature of CAH and the limitations and risks of chronic GC therapy, new treatments are urgently needed for patients with CAH. Corticotropin-releasing factor type-1 (CRF_1) receptor antagonism may provide a means of decoupling the treatment goals of CAH – physiologic cortisol replacement and androgen control. The ability to control androgen levels through ACTH modulation could reduce patients' dependence on high-dose GCs and alleviate the challenges associated with hyperandrogenemia and supraphysiologic GC exposure.

1.1.3. Overview of Tildacerfont

Tildacerfont, a potent and highly selective small-molecule antagonist of CRF_1 receptors, is being studied for the treatment of CAH on the basis of its ability to block the CRF_1 receptors in the pituitary gland. This blockage may decrease 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 approximately physiologic replacement levels.

Tildacerfont has been tested in 6 completed Phase 1 studies using single doses ranging from 2 to 800 mg or multiple doses ranging from 50 to 200 mg QD. Once daily dosing has been studied in 2 completed Phase 2 studies using multiple doses ranging from 200 to 1000 mg QD for 2 weeks, and up to 400 mg QD for 12 weeks. Twice daily (BID) dosing of tildacerfont has been well tolerated in adults with CAH in previous clinical studies at doses up to 200 mg BID for 2 weeks. Safety data show that tildacerfont has been generally well tolerated in all clinical studies to date, with no related serious adverse events (SAEs) in current on-going studies.

Data from the 2 completed Phase 2 studies in adults 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.

Tildacerfont's mechanism of action is well-suited to potentially address the underlying pathophysiology driving excess adrenal androgen production in CAH as it blocks CRF_1 receptor engagement at the level of the anterior pituitary, and as demonstrated in completed clinical studies in adults, reduces the levels of not only ACTH, but also downstream resultant adrenal androgens and androgen precursors (17-OHP and A4) in patients with CAH. Thus, tildacerfont has the potential to effect normalization of androgen levels while allowing for GC replacement at approximately physiologic dose levels.

Nonclinical studies and clinical studies of tildacerfont are summarized in Section 1.3 and full details are available in the IB.

1.2. Study Rationale

1.2.1. Rationale for the Study Design

SPR001-205 is an open-label dose ranging phase 2 study to evaluate the potential of tildacerfont to reduce androgen levels and GC burden in participants ages 2-years and older with classic CAH. SPR001-205 will be the first study of tildacerfont in children and will be used to assess safety and to determine the consistency of preliminary tildacerfont pharmacokinetics (PK) in pediatrics with those simulated in a physiologically based pharmacokinetic (PBPK) model. In Cohorts 1-3, the study will also characterize changes in androgen levels over 12 weeks of treatment, and the ability to reduce GC doses based on A4 normalization. In Cohorts 4-9, it will characterize changes in androgen levels over the first 4 weeks of treatment with BID dosing. An optional extension period will provide additional treatment with tildacerfont to provide long-term safety data for up to two years.

In completed Phase 2 studies in adult participants with classic CAH, tildacerfont exhibited an acceptable safety profile and proof-of-concept efficacy in reducing ACTH, 17-OHP, and A4 levels at effective doses, which support the continued clinical development of tildacerfont for the treatment of CAH.

As the first study of tildacerfont in a pediatric CAH population, the primary objective is to gain knowledge of the safety profile of tildacerfont. Secondary objectives of the study are to characterize the efficacy of tildacerfont in reducing A4 levels after 4 weeks of treatment (all cohorts) and reducing GC doses based on A4 normalization over 12 weeks of treatment (Cohorts 1-3), as well as comparing plasma concentrations of tildacerfont in pediatric participants with those of a simulated PBPK model. Exploratory objectives include assessing changes from baseline in levels of ACTH, 17-OHP, A4, testosterone, and 11-ketotestosterone (11KT).

In the interest of progressing cautiously, the study's cohorts are defined by decreasing age in addition to ascending tildacerfont dose. Dosing will begin in Cohort 1 with participants in the older age group of 11 to 17 years and with the lowest dose level. Subsequent cohorts will be initiated only after a recommendation from the Data Monitoring Committee (DMC) is reviewed by the Sponsor. The final decision to progress cohorts will be made by the Sponsor. Cohort 2 will continue with participants in the older pediatric age group but dosing at a higher level (no greater than the weight-adjusted adult equivalent of 200 mg once daily [QD]). Cohort 3 will dose no higher than Cohort 2 but enroll participants in the younger age group of 2 to 10 years. An optional interim dose cohort (Cohort 1a) may be enrolled only if needed per DMC recommendation and Sponsor decision, in the event of a safety concern in participants in Cohort 1 (Figure 1).

Due to changing HPA axis dynamics across developmental stages (associated with changing GC requirements) and the fact that younger children have increased liver CYP enzyme activity (which may lead to increased tildacerfont clearance), alternative dosing regimens will also be explored, including BID dosing in Cohorts 4-9. Cohorts 4 and 5 will include adult patients (to further establish safety), Cohorts 6, 8 will include children 11-17 years of age, and Cohort 7 and 9 will include children 2-10 years of age. All cohorts including doses above 200 mg QD will be adaptive, so that the determination to initiate a cohort, and at what dose, may be determined by the Sponsor, within the guidelines of the protocol, based on recommendations by the DMC and emerging safety and exposure data (Figure 2).

Cohort 4 (adults) and Cohort 6 (11-17 years) will initiate concurrently at doses of 200mg BID. Initiation of 200mg adult equivalent BID in adolescents is supported by the prior study of 200mg QD in Cohort 2 and the prior study of doses up to 200mg BID and 1000mg QD in adults (SPR001-201).

Following DMC recommendation, Cohorts 5 and 7 may be initiated concurrently. Cohort 5 will include adults receiving either 300 or 400mg BID, and Cohort 7 will consist of children 2-10 years old receiving 200mg adult equivalent BID. If 300m BID is pursued in Cohort 5, a DMC meeting may be called to review safety data of 5 participants and make a recommendation regarding the potential enrollment of another 5 participants at a dose of 400mg.

Cohorts 8 and 9 may be initiated to investigate either a 300 or 400 mg adult equivalent BID dose (depending on DMC recommendation and Sponsor decision) in children (2-10 and 11-17 years respectively). If Cohort 8 is initiated, the DMC will convene once safety data is available for 4 participants and make a recommendation regarding initiation of Cohort 9. If 300mg equivalent BID is pursued in either cohort and escalation to 400mg is considered, a DMC meeting will be called to review safety data of 5 participants and make a recommendation regarding the potential enrollment of another 5 participants at a dose of 400mg equivalent BID. Thus Cohorts 8 and 9 may enroll up to 10 participants for each cohort (Table 1)**.**

1.2.2. Study Population

The study is expected to enroll approximately 20 children across Cohorts 1, 2, and 3, specifically 10 participants in the 11- to 17-year-old age group (i.e., 5 participants in Cohort 1 and 2) and 10 in the 2- to 10-year-old age group (i.e., 10 participants in Cohort 3). If the optional Cohort 1a is initiated, Cohorts 1-3 may, however, enroll up to approximately 25 children.

This study will also enroll approximately 5 adults aged ≥18 years in Cohort 4 and 5-10 adults in Cohort 5. Therefore, up to approximately 15 adults may be enrolled. Cohorts 6 and 7 will enroll approximately 5 children each in the 11-17- and 2-10-year age groups, respectively. If Cohorts 8 and 9 are initiated, each will also enroll approximately 5-10 children. Therefore, up to 30 children may be enrolled in the BID dosing cohorts (Table 1).

1.2.3. Rationale for the Study Drug Dosing

Tildacerfont has been tested in 6 completed Phase 1 studies using single doses ranging from 2 to 800 mg or multiple doses ranging from 50 to 200 mg QD. Once daily dosing has been studied in 2 completed Phase 2 studies using multiple doses ranging from 200 to 1000 mg QD for 2 weeks, and up to 400 mg QD for 12 weeks. BID dosing of tildacerfont has been well tolerated in adults with CAH in previous clinical studies at doses up to 200 mg BID for 2 weeks. Safety data show that tildacerfont has been well tolerated in all clinical studies to date, with no related serious adverse events (SAEs) in any of the completed or the on-going SPR001-205 study. One SUSAR that included worsening diarrhea and enteritis in the context of acute adrenal insufficiency and a history of colitis was reported in SPR001-203, one of two ongoing placebo-controlled trials in adults with CAH.

As there is a food effect with tildacerfont, clinical development has been and continues to be conducted in the fed state. The clinical efficacy/pharmacodynamic (PD) data show CRF_1 receptor target engagement (reductions in ACTH) and reductions in key adrenal pre-cursors and hormones (17-OHP and A4) in participants with CAH dosed for 2 weeks with tildacerfont at 200 mg/day or higher. A 1-compartment PK model with first-order absorption and elimination was fit to PK data from Study SPR001-201 and used to estimate the steady-state exposure for each participant at each dose.

The adult exposure levels observed after 2 weeks of treatment were extrapolated to pediatric participants based on body weight and age for this study using a PBPK approach based on healthy adults. The PBPK model was based on *in vitro* and *in vivo* information on the metabolism and PK of tildacerfont and was validated using the plasma concentration-time profiles in healthy adults in the fed state. To account for differing CYP3A4 expression by age, the Upreti ontogeny profile was used in the pediatric dose predictions in three age groups, 2 to 5, 6 to 10, and 11 to 17 (Upreti and Walhstrom 2016). Pediatric doses on a mg/kg basis were predicted by age group to correspond to the adult exposures at the same dose levels. Within the lower dose cohorts (50 mg and 100 mg), dose bands were constructed such that participants would not receive a dose greater than 20% over the predicted mg/kg conversion. Weight bands were constructed such that participants in higher dose cohorts would not receive a dose greater than 10% over the predicted mg/kg conversion of the corresponding adult dose.

Preliminary PK data from Cohorts 1-3 show that the PBPK model overestimates drug exposure in children, such that the weight-based adult equivalent doses utilized in the children do not provide the exposures observed in adults. Additionally, an inverse relationship between age and exposure is apparent. This may be due to differences in drug metabolism across developmental stages, specifically CYP enzyme activity which is the primary driver of tildacerfont elimination. CYP enzyme activity peaks in early childhood and declines into adulthood. Consequently, children sometimes require relatively higher doses than adults to achieve optimal exposures of drugs that are eliminated by CYP-dependent metabolism (i.e., the Upreti ontogeny profile may not have adequately adjusted for physiologic differences that impact tildacerfont exposure).

Higher doses and more frequent administration of tildacerfont may support increased and more consistent exposure in spite of the more rapid elimination in children. Further dose exploration is supported by the fact that no safety signal has been observed in Cohorts 1-3 at the time of this amendment, which includes 30 pediatric participants on doses up to 200mg adult equivalent QD for up to 24 weeks (1Nov23). Additionally, the 200mg QD dose which is the dose being used in the on-going adult CAH studies have a safety margin of 13.7 relative to the NOAEL from pre-clinical studies. This margin is expected to be greater in children because the exposures observed in SPR001-205 have been substantially lower than those observed in the adult studies.

The maximum planned dose is 400 mg BID, subject to adjustment based on safety and PK data obtained during this study. The design of this amendment allows for the evaluation of exposure in adults starting at 200mg BID and continuing (per DMC recommendation) with dosing up to 400mg BID, such that all new dosing regimens have been or will be tested in adults prior to children. Additionally, pediatric exposure at 200mg BID can be evaluated prior to increasing to up to 400mg BID in children. Given that pediatric exposures are observed to be less in children than adults, this stepwise approach optimizes the ability to ensure that no pediatric exposures exceed those previously studied in adults.

Pediatric weight-based tildacerfont dose levels equivalent to doses of 50 mg, 100 mg, 200 mg QD, as well as 200mg, 300 mg, and 400 mg BID in adults are defined in Table 2 by age group.

1.3. Risk/Benefit Assessment

Tildacerfont has been generally well tolerated at effective doses and has demonstrated the ability to reduce ACTH and downstream adrenal androgen production in adult patients with CAH and elevated adrenal androgen levels in Phase 2a studies. The most frequently reported non-procedural associated adverse events (AEs) were headache and diarrhea. No drug-related SAEs have been reported in completed clinical studies to date.

Potential clinically significant risks identified in the pre-clinical program include histopathological changes in the thyroid gland and male reproductive tract, developmental toxicity and mild, possibly treatment-related trends in increased Fridericia-corrected QT interval (QTcF) duration. However, no corresponding functional decline in thyroid or male reproductive biochemical assessments has been observed in human studies completed to date, nor have any cardiovascular safety concerns been noted with either vital signs or electrocardiogram (ECG) monitoring. Developmental toxicity has not been evaluated in human clinical trials.

Hepatic effects were also noted in the pre-clinical program, and reversible liver enzyme elevations have been observed in clinical studies.

Additional details of known and potential risks of tildacerfont are provided in the IB. Study SPR001-205 has incorporated multiple design elements to mitigate these potential risks including extensive laboratory assessments (Section 7.1.5), an independent Hepatic Adjudication Committee to assess potential liver issues, ECG monitoring (Section 7.1.4), contraception requirements (Section 4.2.3), and stopping criteria (Section 6.1).

As tildacerfont is metabolized by CYP3A4, drug-drug interaction risk necessitates the prohibition of concomitant use of known moderate to strong inducers or inhibitors of CYP3A4. Moreover, as tildacerfont is a moderate inhibitor of CYP3A4, drugs that are sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 and/or breast cancer resistance protein (BCRP) must be avoided; for sensitive substrates or narrow-therapeutic-range substrates of BCRP in the absence of CYP3A4, cautionary use is advised with separation of at least 10 hours from tildacerfont and ongoing assessment for loss of efficacy.

2. OBJECTIVES AND ENDPOINTS

COHORTS 1-3 (12-week Treatment)	
Objectives	**Endpoints**
Primary	
To evaluate the safety of tildacerfont in participants with CAH	AEs and SAEs
Secondary	
To determine the efficacy of tildacerfont on disease control or reduction of GC use in participants with classic CAH during 12 weeks of treatment	Proportion of participants who achieve a reduction in A4 or reduction in GC dosing during treatment period
To determine the efficacy of tildacerfont on disease control in participants with classic CAH after 4 or 12 weeks of treatment	Proportion of participants with elevated baseline A4 who achieve a reduction in A4 at Week 4
	Proportion of participants with elevated baseline A4 who achieve A4 normalization at Week 4 or Week 12
To determine the consistency of preliminary tildacerfont PK in participants with those simulated in a PBPK model	Tildacerfont plasma concentrations will be compared with the current PBPK simulation for consistency
Exploratory	
To explore changes in pharmacodynamic (PD) biomarkers in participants with CAH	Change from baseline in adrenocorticotropic hormone (ACTH), 17hydroxyprogesterone (17-OHP), A4, testosterone, and 11-ketotestoterone (11KT)
COHORTS 4, 5, 6, 8, 7, and 9 (4-week Treatment)	
Objectives	**Endpoints**
Primary	
To evaluate the safety of tildacerfont in participants with CAH	Adverse events (AEs) and serious adverse events (SAEs)

Secondary	
To determine the efficacy of tildacerfont on disease control in participants with classic CAH after 4 weeks of treatment	Proportion of participants who achieve reduction in androstenedione (A4) at Week 4
	Proportion of patients who achieve A4 normalization at Week 4.
To determine the consistency of preliminary tildacerfont pharmacokinetics (PK) in participants with those simulated in a physiologically based PK (PBPK) model	Tildacerfont plasma concentrations will be compared with the current PBPK simulation for consistency
Exploratory	
To explore changes in pharmacodynamic (PD) biomarkers in participants with CAH	Change from baseline in adrenocorticotropic hormone (ACTH), 17hydroxyprogesterone (17-OHP), A4, testosterone, and 11-ketotestoterone (11KT)
EXTENSION (Cohorts 1-9)	
Objectives	**Endpoints**
Primary	
To evaluate the safety of tildacerfont in participants with CAH	AEs and SAEs
Secondary	
To determine the efficacy of tildacerfont on reduction of glucocorticoid (GC) use in participants with classic CAH after 4 weeks or 12 weeks of treatment	Proportion of participants who achieve reduction in glucocorticoid (GC) dosing (beyond 12 weeks for Cohorts 1-3 and beyond 4 weeks for Cohorts 4-9)
	Proportion of participants who achieve approximately physiologic GC dosing (≤ 11 $g/m^2/d$)
To determine the efficacy of tildacerfont on disease control in participants with classic CAH	Proportion of participants with elevated A4 at completion of treatment period (Week 12 for Cohorts 1-3 and Week 4 for Cohorts 4-9) who achieve a reduction in A4
	Proportion of participants with elevated A4 at completion of treatment period who achieve A4 normalization

Exploratory	
To explore changes in pharmacodynamic (PD) biomarkers in pediatric participants with CAH	Change from baseline in adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17-OHP), A4, testosterone, and 11-ketotestoterone (11KT), (at Week 4 for all cohorts and Week 12 for Cohorts 1-3)
To explore the impact of tildacerfont on skeletal maturation	Change from baseline in predicted adult height

3. STUDY DESIGN

3.1. Overall Design

This is a Phase 2, open-label, dose-ranging study designed to provide safety, efficacy, and PK of tildacerfont, as well as the impact of tildacerfont on adrenal androgens and GC requirements in participants with classic CAH.

Three staggered cohorts (Cohorts 1-3) are planned to investigate QD dosing over 12 weeks of treatment, with an additional optional Cohort 1a, dependent on accumulating safety data. The study is expected to enroll approximately 20 children across the first 3 cohorts (i.e., Cohorts 1, 2, and 3), 10 in the 11-to 17-year age group and 10 in the 2-to 10- year age group. If the optional Cohort 1a is initiated (up to 5 participants), however, Cohorts 1 to 3 may enroll up to 25 children total, 15 in the 11-to 17-year-old age group and 10 in the 2-to 10-year-old age group.

Up to an additional six cohorts (Cohorts 4-9) are planned to investigate BID dosing over 4 weeks of treatment. The study will also enroll up to approximately 15 adults aged ≥18 years across Cohorts 4 and 5; and up to approximately 30 children across 4 additional cohorts [up to 15 in the 11- to 17-year age group (Cohorts 6 and 8) and up to 15 in the 2- to 10-year age group (Cohorts 7 and 9)].

If all possible doses are studied, total sample size of this study may be up to approximately 55 children and 15 adults (Table 1).

Participants enter the study on their current GC regimen (note: dexamethasone is excluded). In Cohorts 1-3, GC dose may be adjusted based on A4 levels at specified weeks and at any visit during the extension. In Cohorts 4-9, there will be no GC adjustment during the 4-week study period, but GC doses can be adjusted for those who participate in the optional extension at Week 4 and any subsequent visit. For further details refer to Section 5.3.1.2.

Cohorts 1 to 3:

Cohorts 1, 1a (if indicated), and 2 will include children ages 11- to 17-years old (up to approximately 5 participants in each cohort), and Cohort 3 (up to approximately 10 participants) will include children ages 2- to 10-years old.

For these cohorts, the study will last approximately 18 weeks including a 2-week Screening Period, a 12-week Treatment Period and a Safety Follow-up visit 30 days after the last dose of study drug (during the Treatment Period). Participants may continue in an extension period upon completion of the 12-week Treatment Period. If participants enroll in the extension study after the 12-week Treatment Period, the Safety Follow-up Visit will occur 30 days after the last dose in the extension.

Dosing will begin in Cohort 1 with participants 11- to 17- years of age dosing at the adult equivalent of 50 mg QD. Cohort 2 will continue in the same 11– to 17-year-old age group but dosing at 200 mg QD. Cohort 3 will enroll participants 2-to 10-years of age but dose no higher than Cohort 2. If safety concerns are identified in the Cohort 1 participants, an interim dose Cohort 1a may be initiated prior to proceeding to Cohort 2 dosing.

Cohort 1 will include up to approximately 5 participants who will receive a tildacerfont dose that is equivalent to the adult dose of 50 mg. Data from the first 2 participants will be considered sentinel and will inform a safety review by an independent DMC. After reviewing the first 2 weeks of data from the sentinel participants, the DMC will make one of three recommendations regarding continuing enrollment:

1) If data suggest the dose was well-tolerated by the sentinel participants, Cohort 2 (200 mg equivalent) will be initiated.
2) If a safety concern is identified, for example, a sentinel participant experiences an individual stopping criterion or a suspected unexpected serious adverse reaction (SUSAR), the DMC may withhold their recommendation until additional safety data are available from the additional 3 participants in Cohort 1.
3) The DMC may also recommend initiating an interim cohort (Cohort 1a) of up to 5 participants to evaluate the same or a different dose (e.g., 50 or 100 mg adult equivalent) before proceeding to Cohort 2 (200 mg equivalent). After reviewing 2 weeks of safety data from Cohort 1a sentinel participants (i.e., first 2 participants), the DMC may recommend initiating Cohort 2. However, if safety concerns are identified, the DMC may recommend reviewing safety data from an additional 3 patients prior to recommending/not recommending initiation of Cohort 2. The DMC will review safety data from Cohort 1a participants and recommend a dose increase to Cohort 2, or initiation of Cohort 3 at the dose used in Cohort 1a.

Cohort 2 will receive the equivalent of the adult dose of 200 mg. Cohort 2 may enroll up to approximately 5 participants. This allows for up to approximately 10 planned participants in the 11- to 17-year-old age group across Cohorts 1, and 2, and up to approximately 15 participants if Cohort 1a is initiated.

Following DMC review of safety data from the first 2 weeks for sentinel participants in Cohort 2 (or Cohort 1a, if utilized), Cohort 3 may be initiated. Cohort 3 will dose no higher than the highest dose found to be safe in 11-to 17-year-olds but enroll up to approximately 10 participants in the younger age group of 2 to 10 years. There will be a DMC) review of data from Cohort 3 regarding the initiation of further cohorts with BID dosing (Table 1, Figure 1).

Cohorts 4 to 9:

All participants in Cohorts 4 to 9 will be enrolled for a 4-week study period. Before escalating to the next highest dose cohort, the DMC will evaluate a total of 4 sentinel participants from the combined cohorts (to initiate a new dosing regimen in a pediatric cohort, data from at least 2 pediatric sentinels must be included in the review).

The study will last approximately 10 weeks including a 2-week Screening Period, a 4-week Treatment Period and a Safety Follow-up visit 30 days after the last dose of study drug). Participants may continue in an extension period upon completion of the 4-week Treatment Period. If participants enroll in the extension after the 4-week Treatment Period, the Safety Follow-up Visit will occur 30 days after the last dose in the extension. Cohorts 4 and 5 will include adults aged ≥18 years (up to approximately 5 participants in Cohort 4 and 10 participants in Cohort 5). The 10 participants that may be evaluated in Cohort 5 is to allow for the possibility of more than one dose tested (i.e., 300mg or 400mg BID – per DMC recommendation). Cohorts 6 and 8 will include children ages 11 to 17 years old (up to approximately 5 participants in each cohort) and Cohorts 7 and 9 will include children ages 2 to 10 years old (up to approximately 5 participants in each cohort). Cohorts 8 and 9 may include approximately 5 additional participants each if more than one dose is tested (i.e., 300mg and 400mg equivalent BID). For example, if 5 children are treated with 300mg BID in Cohort 8, the DMC may review safety data from all 5 after 4 weeks of treatment and make a recommendation regarding enrolling another approximately 5 children at 400mg BID (Table 1, Figure 2).

Cohorts 4 and 6 will begin simultaneously with a dose of 200 mg BID in participants aged ≥18 years and 200 mg adult equivalent BID in participants aged 11-17 years (200 mg BID has been previously evaluated in adults in study SPR001-202).

The DMC will convene once 4 weeks of safety data is available for 4 sentinels from Cohorts 4 and 6 combined. After reviewing data from these 4 participants (in addition to all other available safety data), the DMC will make a recommendation regarding initiation of Cohorts 5 and 7.

Cohort 5 will enroll adult participants at 300 or 400mg BID (per DMC recommendation) and will provide safety data in adults to support the administration of higher BID doses (i.e., up to 400mg BID) in children and adolescents. Cohort 7 may begin simultaneously with Cohort 5 and will enroll children aged 2-10 years at a dose of 200mg adult equivalent BID.

Once safety data are available for Cohort 5 and 7 sentinels, the DMC will convene and make a recommendation regarding initiation of pediatric cohorts at doses >200mg BID. The Sponsor will then decide whether to initiate Cohort 8 at a dose up to 400mg BID. Subsequently, the DMC may review data from 4 sentinels from Cohort 8 and make a recommendation regarding further dose increase in the younger age group. Sponsor may then decide whether to initiate Cohort 9 at a dose up to 400mg BID.

A sparse serial blood sampling approach for PK will also be used in Cohorts 4 to 9 on Day 1 (Visit 2) and Week 2/Day 14 (Visit 3). Blood samples for tildacerfont concentration should be obtained pre-dose and between 0.5 - 1.5 hours and 3 - 5 hours post dosing. At these visits, participants will dose in clinic with a meal at 8 am (± 1 hour).

All participants in Cohorts 4-9 will receive open-label tildacerfont for the 4-week treatment period, after which they may be offered optional continued treatment if the clinical Investigator believes it is in the participant's best interest. Once enrolled in the extension period, participants may adjust tildacerfont dose up to the highest dose recommended by the DMC per age group at the Investigator's discretion.

Table 1. Study Cohorts

Cohort	Age	Corresponding Adult Dose	Subject Numbers	Treatment Duration
1	11- to 17-years	50 mg QD	5	12 Weeks
1a[a]	11- to 17-years	To be determined based on DMC recommendation (50 or 100 mg QD)	5	
2	11- to 17-years	200 mg QD	5	
3	2- to 10-years	50 mg QD, 100 mg QD, OR 200 mg QD	10	
4	≥18-years	200 mg BID	5	4 weeks
5	≥18-years	300 and/or 400 mg BID	5+5[c]	
6	11- to 17-years	200 mg BID	5	
8[b]	11- to 17-years	300 and/or 400 mg BID	5+5[c]	
7	2- to 10-years	200 mg BID	5	
9[b]	2- to 10-years	300 and/or 400 mg BID	5+5[c]	
			Up to 70 subjects total	

Abbreviations: BID=twice daily; DMC=Data Monitoring Committee; QD=once daily.

[a] Cohort 1a is an optional interim dose cohort that may be enrolled only if needed per DMC recommendation and Sponsor decision, in the event of a safety concern in participants in Cohort 1.

[b] Cohort 8 and 9 are adaptive cohorts that may be enrolled based on emerging safety data and per DMC and Sponsor recommendation/approval.

[c] +5 allows for the option of dosing 300mg before or after 400 mg Cohort is initiated if indicated by the DMC

A schema of the study design is presented in Figure 1 for Cohorts 1, 1a, 2, and 3; and in Figure 2 for Cohorts 4, 5, 6, 7, 8 , and 9.

Figure 1. Overall Study Design for Cohorts 1, 1a, 2, and 3

Cohort	Age (years)	Corresponding Adult Dose
1	11 to 17	50 mg QD
1a*	11 to 17	To be determined based on DMC recommendation
2	11 to 17	200 mg QD
3	2 to 10	50 mg QD, 100 mg QD, OR 200 mg QD

*Cohort 1a is an optional interim dose cohort that may be enrolled only if needed per DMC recommendation and Sponsor decision, in the event of a safety concern in sentinel participants in Cohort 1.

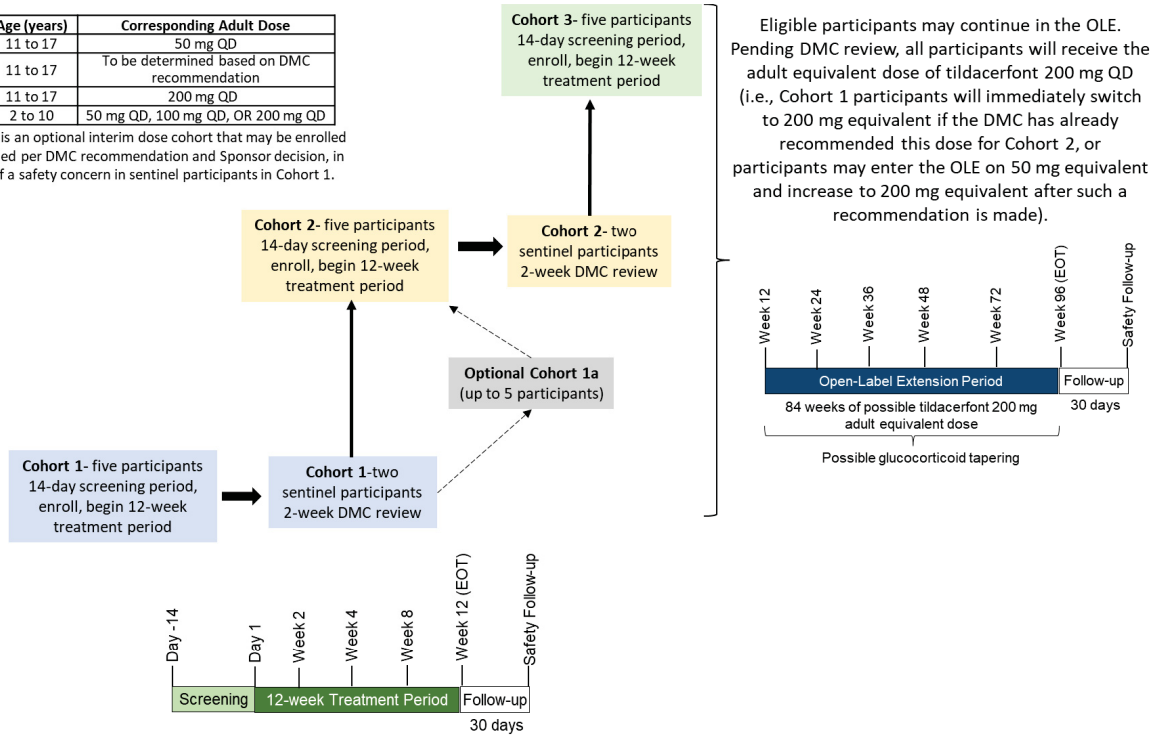
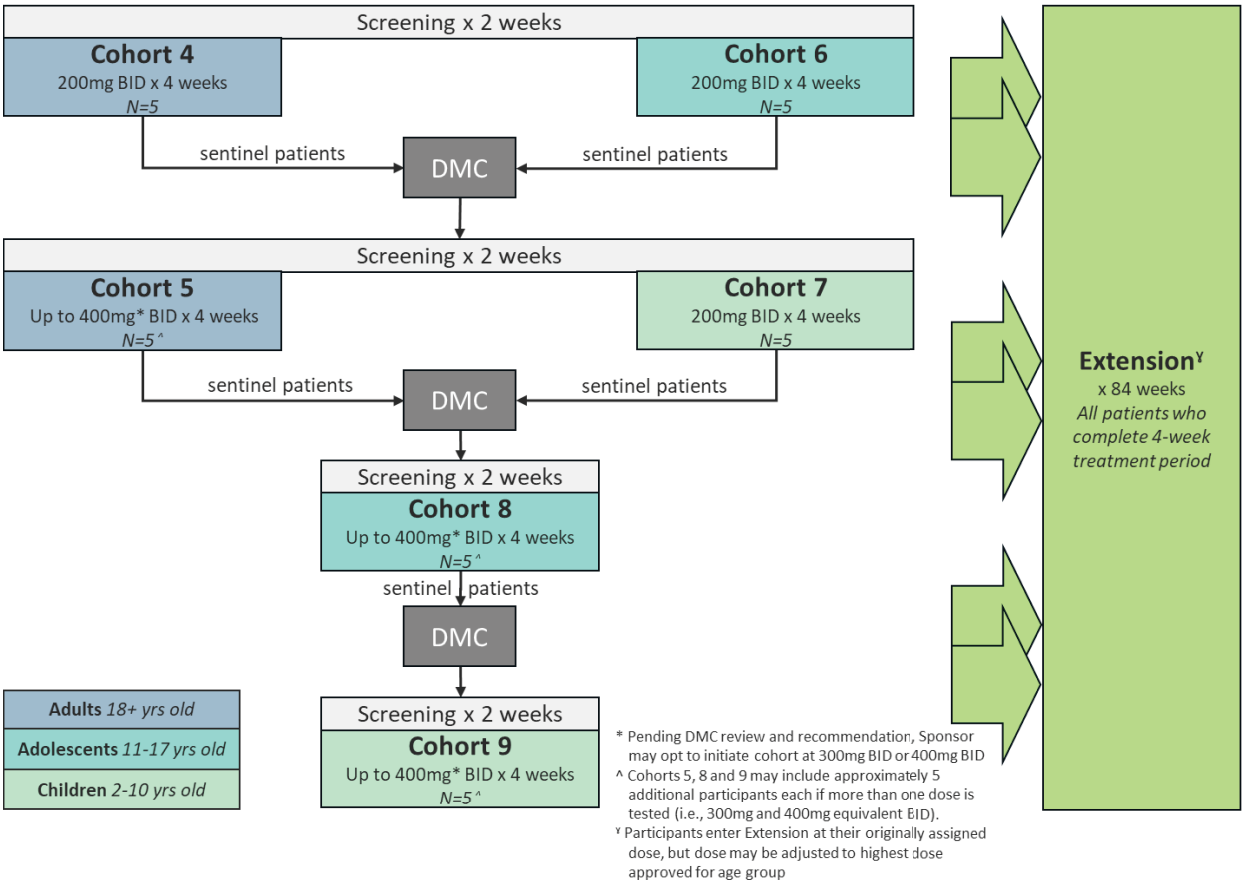


Figure 2. Overall Study Design for Cohorts 4, 5, 6, 8, 7, and 9



Note: Any participant enrolled under protocol amendment 3 may be re-consented to protocol amendment 4 and receive the 12-week treatment course; however, because they will have already contributed PK data, they will not be required to have blood draws for tildacerfont concentration on Days 1 and 14 between 0.5 to- 1.5 hours and between 3 to 5 hours post dosing. Additionally, any participant enrolled under amendment 4 (or any other tildacerfont study) may be re-consented and enrolled under protocol amendment 5.

3.1.1. Data Monitoring Committee

An independent DMC will review the available data on an ongoing basis throughout the study and before initiating a new cohort. The DMC will be composed of independent reviewers who are not involved in the conduct of the study. The DMC will advise the Sponsor of any trends or safety issues that may impact the study or study participants. In particular, the occurrence of any clinically significant AE (including but not limited to SAEs, AEs leading to study drug discontinuation/study withdrawal, dose-limiting toxicities [DLTs], and adverse events of special interest [AESIs], all considered at least possibly related to study drug) will receive special consideration (see Section 7.2.5). The Sponsor will make final decisions concerning the continuation, modification, or termination of the trial. The DMC's scope of responsibility, membership, confidentiality, and procedures will be established in a separate DMC charter. Three DMC reviews are planned during and upon completion of Cohorts 1-3. Three additional DMC reviews are planned during Cohorts 4-9. Ad hoc DMC meetings may be called by the Sponsor or the DMC Chair (Figure 2).

For Cohorts 1-3, the DMC will review safety data from a minimum of 2 sentinel participants for 2 weeks at each meeting. For Cohorts 4-9, the DMC will review safety data from a minimum of 4 sentinel participants at each meeting, but it is not required that 2 come from each cohort. However, to initiate a

new dosing regimen in a pediatric cohort, data from at least 2 pediatric sentinels must be included in the review.

3.1.2. Study Visits

Each participant will undergo a Screening Period of up to approximately 14 days, a 12-week (Cohorts 1 to 3) or 4-week Treatment Period (Cohorts 4 to 9), and a 30-day Safety Follow-up Period. The Screening Period may be extended as approved by the Sponsor and/or contract research organization (CRO) designee. The Schedule of Activities for the study is provided in Appendix 1 and Appendix 3 for Cohorts 1 to 3 and Cohorts 4 to 9, respectively. The Schedule of Activities for the extension is in Appendix 2 and Appendix 4, respectively.

3.1.2.1. Visit 1 (Screening)

Initial Screening will be conducted as an outpatient visit at approximately Day -14; the screening window may be extended with Sponsor/Medical Monitor (MM) approval. The following activities will be performed:

- Informed consent/assent and/or parent/legal guardian permission, as applicable (prior to undergoing any study procedures)
- Assessment of participant eligibility (Inclusion/Exclusion Criteria)
- Review of demographics, medical history, and medications (both current and from the past year)
- Hepatitis B, C, and human immunodeficiency virus (HIV) screening
- Pregnancy test for females of childbearing potential (FOCP) (serum)
- Screening/safety labs (see Appendix 1 and Appendix 3)
- Urinalysis
- Vital signs: blood pressure, pulse rate, body temperature, respiration rate, weight, and height (height is only measured during the Screening Visit).
- Physical exam (abbreviated/directed)
- 12-lead ECG
- Baseline Suicidality Questionnaire- Columbia–Suicide Severity Rating Scale (C-SSRS) (for participants aged ≥6 years only)
- Baseline Depression and Anxiety Questionnaires (Patient Reported Outcomes Measurement Information System [PROMIS] (for participants aged ≥5 years only) or Survey of Well-being of Young Children [SWYC] depending on age of participant)
- Bone age and predicted adult height calculated from x-ray image of left hand and wrist (if deemed appropriate by the principal investigator). Alternatively, a calculation using historical data is acceptable if image is within 6 months prior to screening. An x-ray may be repeated at the discretion of the Investigator. This will not be performed in adults (Cohorts 4 & 5).

3.1.2.2. Visit 2 (Day 1)

Visit 2 will be conducted as an outpatient visit during which a supervised first dose of tildacerfont will be administered after completion of a morning meal. The following activities will also be performed during the visit:

- Re-confirm participant meets inclusion/exclusion criteria
- Review concomitant medications for any changes
- Pregnancy test for FOCP (urine)
- For Cohorts 1, 2, 4, 5, 6, 7, 8, and 9 (and 1aif indicated), serial blood samples will be collected at 3 timepoints: pre-dose (prior to GC dosing and tildacerfont dosing), 0.5 to 1.5 hours post-GC and tildacerfont dose, and 3 to 5 hours post-GC and tildacerfont dose. After the pre-dose sample, participants will receive a meal and take their morning GC dose and study drug. Fasting is not required. Blood samples will be used to assess tildacerfont concentrations and to compare to the PBPK model, as well as PD markers including ACTH, 17-OHP, A4, testosterone, and 11KT.
    - Note: Cohorts 1 and 2 (and 1a if indicated) will receive study drug in the mornings for the first 14 days, so they will continue to take study drug at home with a morning meal until Day 14/Visit 3.
- For Cohorts 3 only one pre-dose sample will be drawn, after which participants will receive a meal and their morning GC dose and study drug. They should be observed for approximately 1 hour after receiving study drug.
    - Note: Cohort 3 will only receive the first dose of study drug in the morning to allow clinical observation. They will switch to home dosing with an evening meal on Day 2.
- Vital signs: blood pressure, pulse rate, body temperature, respiration rate, and weight (pre-dose)
- Physical exam (full)
- Safety labs (pre-dose, see Appendix 1 and Appendix 3)
- Dispense study drug (12-week or 4-week supply, depending on cohort)
- Assess for AEs

3.1.2.3. Visit 3 (Week 2; Day 14 ±3 days)

Visit 3 will be conducted as an outpatient visit. Cohorts 1, 2, 4, 5, 6, 7, 8, and 9 (and 1a if indicated) will receive study drug and morning GC dose after completion of a morning meal. Cohort 3 will have received study drug the evening prior and will not require supervised dosing or a meal. Note: Cohort 1, 2, 4, 5, 6, 7,8 and 9 (and 1a, if indicated) participants will need to bring study drug to the visit for in-clinic dosing to collect tildacerfont concentrations. The following activities will also be performed during the visit:

- Review concomitant medications for any changes
- Pregnancy test for FOCP (urine)
- Safety labs (predose; see Appendix 1 and Appendix 3)
- For Cohorts 1, 2, 4, 5, 6, 7, 8, and 9 (and 1a, if indicated), serial blood samples will be collected at 3 timepoints: pre-dose (prior to GC dosing and tildacerfont dosing), 0.5 to 1.5 hours post-GC and tildacerfont dose, and 3 to 5 hours post-GC and tildacerfont dose. After the pre-dose sample, participants will receive a meal and take their morning GC dose and study drug. Fasting is not required. Blood samples will be used to assess tildacerfont concentrations and to compare to the PBPK model, as well as PD markers, including ACTH, 17-OHP, A4, testosterone, and 11KT.

  - Note: Cohorts 1 and 2 (and 1a if indicated) will switch to evening dosing with a meal at home on Day 15.

- For Cohorts 3, only one pre-dose sample will be drawn, after which participants will receive their morning GC dose and tildacerfont dose. Fasting is not required. Blood samples will be used to assess tildacerfont concentrations as well as PD markers including ACTH, 17-OHP, A4, testosterone, and 11KT.
- Cortisol
- Urinalysis (pre-dose)
- Vital signs: blood pressure, pulse rate, body temperature, respiration rate, and weight (pre-dose)
- Physical exam (abbreviated/directed)
- 12-lead ECG (pre-dose)
- Suicidality Questionnaire- C-SSRS since last visit (participants aged ≥6 years only)
- Depression and Anxiety Questionnaires (PROMIS or SWYC depending on age of participant)
- Study drug accountability
- Assess for AEs

3.1.2.4. Visit 4 (Week 4 ±3 days) (EOT for Cohorts 4-9)

Visit 4 will be conducted as an outpatient visit. The following activities will be conducted:

- Review concomitant medications for any changes
- Pregnancy test for FOCP (urine)
- Safety labs (see Appendix 1 and Appendix 3)
- Pharmacodynamics (ACTH, 17-OHP, A4, testosterone, and 11KT) drawn prior to GC dosing at approximately 8 AM (±1 hour). Fasting is not required.
- Cortisol
- Tildacerfont concentration (single sample) drawn prior to GC dosing at approximately 8 AM (±1 hour). Fasting is not required.
- GC dosing adjustments to be determined after A4 value is measured. Pre-GC A4 is drawn at visit, and once results are received Investigator or designee will call participant and advise regarding any GC dose change. This process applies to all Cohort 1-3 participants and any Cohort 4-9 participants who continue treatment in the extension period.
- Vital signs: blood pressure, pulse rate, body temperature, respiration rate, and weight
- Physical exam (abbreviated/directed)
- Suicidality Questionnaire- C-SSRS since last visit (participants aged ≥6 years only)
- Depression and Anxiety Questionnaires (PROMIS or SWYC depending on age of participant)
- Study drug accountability
- Assess for AEs

- Weight-based tildacerfont dose adjustment, if indicated
- For Cohort 4-9 participants, offer continued treatment in extension at Investigator's discretion, re-consent if applicable.

3.1.2.5. Visit 5 (Week 8 ±3 days) (Cohorts 1-3 only)

Visit 5 will be conducted as an outpatient visit. The following activities will be performed:

- Review concomitant medications for any changes
- Pregnancy test for FOCP (urine)
- Safety labs (see Appendix 1)
- Pharmacodynamics (ACTH, 17-OHP, A4, testosterone, and 11KT) drawn prior to GC dosing at approximately 8 AM (±1 hour). Fasting is not required.
- Cortisol
- Tildacerfont concentration (single sample) drawn prior to GC dosing at approximately 8 AM (±1 hour). Fasting is not required.
- GC dosing adjustments to be determined after A4 value is resulted
- Vital Signs: blood pressure, pulse rate, body temperature, respiration rate, and weight
- Physical exam (abbreviated/directed)
- Suicidality Questionnaire- C-SSRS since last visit (participants aged 6- to 17-years only)
- Depression and Anxiety Questionnaires (PROMIS or SWYC depending on age of participant)
- Study drug accountability
- Assess for AEs

3.1.2.6. Visit 6 (EOT for Cohorts 1-3) (Week 12 ±3 days)

Visit 6 will be conducted as an outpatient visit. The following activities will be performed:

- Review concomitant medications for any changes
- Pregnancy test for FOCP (urine)
- Safety labs (see Appendix 1)
- Pharmacodynamics (ACTH, 17-OHP, A4, testosterone, and 11KT) drawn prior to GC dosing at approximately 8 AM (±1 hour). Fasting is not required.
- Cortisol
- Tildacerfont concentration (single sample) drawn prior to GC dosing at approximately 8 AM (±1 hour). Fasting is not required.
- GC dosing adjustments (for Cohort 1-3 patients who are continuing in the EP) to be determined after A4 value is resulted
- Urinalysis
- Vital signs: blood pressure, pulse rate, body temperature, respiration rate, and weight
- Physical exam (full)

- 12-lead ECG
- Suicidality Questionnaire- C-SSRS since last visit (participants aged 6- to 17-years only)
- Depression and Anxiety Questionnaires (PROMIS or SWYC depending on age of participant)
- Study drug accountability
- Assess for AEs

3.1.2.7. Safety Follow-up Visit Telephone Call (30 days after last dose ±7 days)

Approximately 30 days after the last dose of study drug (post the 12- or 4-week treatment period, depending on cohort, or post the extension), participants will have a final follow-up visit conducted by telephone. Concomitant medications and AEs will be reviewed. If any ongoing safety issues are identified, the participant may be asked to visit the clinic for additional tests, labs, or assessments.

3.1.2.8. Early Termination Visit

Some study participants may need to end their study participation before completing all of the visits. Participants who end their participation before completing the study will be scheduled for an Early Termination Visit. The following activities will be performed at the clinic:

- Review concomitant medications for any changes
- Pregnancy test for FOCP (urine)
- Safety labs (see Appendix 1 and Appendix 3)
- Pharmacodynamics (ACTH, 17-OHP, A4, testosterone, and 11KT) drawn prior to GC dosing at approximately 8 AM (±1 hour). Fasting is not required.
- Tildacerfont concentration (single sample) drawn prior to GC dosing at approximately 8 AM (±1 hour). Fasting is not required.
- Urinalysis
- Vital signs: blood pressure, pulse rate, body temperature, respiration rate, and weight
- Physical exam (full)
- 12-lead ECG
- Suicidality Questionnaire- C-SSRS since last visit (participants aged ≥6 years only)
- Depression and Anxiety Questionnaires (PROMIS or SWYC depending on age of participant)
- Study drug accountability
- Assess for AEs

3.1.2.9. End of Study

A participant is considered to have completed the main study treatment period if they completed Visit 6 (Week 12) or Visit 4 (Week 4), depending on cohort. A participant is considered to have completed the study if the participant has completed the Follow-up Visit. The end of the study is defined as the date of the last Follow-up Visit of the last participant in the study.

3.1.3. Extension Period

Participants who complete the 12- or 4-week treatment period, depending on cohort, may be eligible to continue dosing to complete 2 years on treatment in an extension study. Participants will sign a separate informed consent form at Week 12 or Week 4. Pending DMC review, participants in Cohorts 1 and 1a (if indicated) will receive the adult equivalent dose of 200 mg QD during the extension (i.e., Cohort 1 participants will immediately switch to 200 mg equivalent if the DMC has already recommended this dose for Cohort 2, or participants may enter the extension period on 50 mg equivalent and increase to 200 mg equivalent after such a recommendation is made). If a Cohort 1-3 participant is to dose escalate to the 200 mg equivalent, they may do so at the next scheduled visit or come to the clinic for an unscheduled visit and pick up their new supply of study drug. Participants will receive a follow-up phone call 2 weeks after dose escalation to check for AEs.

Further tildacerfont dose adjustments may occur during the extension on a case-by-case basis at the discretion of the Investigator with Sponsor approval. Any extension participant may receive the highest dose recommended by the DMC for their age group. Dose changes (increase or decrease) may occur at a scheduled visit, an unscheduled visit, or via a phone visit, but any dose escalation > 200mg QD will be followed by safety labs (link to list) within 2-4 weeks of the change. Once all participants are in the extension period, safety- data will be reviewed every 6 months by the DMC. Weight-based dose adjustments may be made at any extension visit, with no follow-up labs required.

For Cohorts 1-3, the first visit of the extension will be Week 12. For Cohorts 4-9, Week 4 will be the first extension visit, followed by extension clinic visits at Weeks 8 and 12 (±2 weeks). Starting at Week 12, all participants will attend clinic visits every 12 weeks (±2 weeks).

Approximately a 12-week supply of study drug, as appropriate, will be dispensed at each visit. Approximately 30 days after the last dose of study drug, participants will have a final follow-up visit conducted by telephone. Concomitant medications and AEs will be reviewed. If any ongoing safety issues are identified, the participant may be asked to visit the clinic for additional tests, labs, or assessments.

The extension study visits will include the following:

- Review concomitant medications for any changes
- Physical exam (abbreviated/directed)
- Vital signs: blood pressure, pulse rate, body temperature, respiration rate, and weight
- Safety labs (see Appendix 2 and Appendix 4)
- Pregnancy test for FOCP (urine)
- Urinalysis (Weeks 48 and 96 only)
- Pharmacodynamics (ACTH, 17-OHP, A4, testosterone, and 11KT) drawn prior to GC dosing at approximately 8 AM (±1 hour). Fasting is not required.
- Tildacerfont concentration (single sample)

- Study drug accountability
- Suicidality Questionnaire- C-SSRS since last visit (participants aged ≥6 years only)
- Depression and Anxiety Questionnaires (PROMIS or SWYC depending on age of participant)
- GC dosing adjustments
- Assess for AEs
- Bone age and predicted adult height calculated from X-ray image of left hand and wrist (every 6 months if deemed appropriate by Investigator, see Appendix 2 and Appendix 4).
- Tildacerfont dose adjustment as needed (based on recommendation of investigator or due to weight-based dosing changes)

4. STUDY POPULATION

4.1. Eligibility Criteria

4.1.1. Inclusion Criteria

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

1. Male and female participants aged 2- to 10-years (Cohorts 3, 7, and 9), 11- to -17 years (Cohorts 1, 1a, 2, 6, and 8), and ≥18 years (Cohorts 4 and 5) at Screening.
2. For participants aged 2 to 5 years, a minimum weight at Screening of 11 kg.
3. Has a known childhood diagnosis of classic CAH due to 21-hydroxylase deficiency (21-OHD) based on genetic mutation in CYP21A2 and/or documented (at any time) elevated 17-OHP and currently treated with hydrocortisone (HC), HC acetate, prednisone, prednisolone, methylprednisolone (or a combination of these). Other types of CAH may be allowed with Sponsor approval.
4. For participants in Cohorts 4-9, 1.2X ULN < A4 < 4X ULN. A4 values outside of this range may be allowed with Medical Monitor (MM) approval.
5. A stable dose of GC replacement for ≥1 month before Screening without evidence of non-adherence (as assessed by Investigator). Weight-based dose adjustments or stress dosing in the month prior to Screening are not exclusionary but should be discussed with the MM.
6. For participants on mineralocorticoid replacement, a stable dose for ≥1 month prior to Screening.
7. For participants on gonadotropin hormone-releasing hormone (GnRH) analogues, a stable dose initiated ≥ 3 months prior to screening.
8. For participants on aromatase inhibitors, a stable dose for ≥ 3 months prior to screening.
9. If sexually active and capable of reproduction, agrees to follow contraception guidelines (Section 4.2.3).
10. Have provided written informed consent or assent, and/or parent/legal guardian permission, as applicable, prior to undergoing any study procedure, including Screening procedures. The participant and/or parent/legal guardian must be able to read and understand all the study procedures.

4.1.2. Exclusion Criteria

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

1. CAH not due to 21-OHD.
2. History of allergy or hypersensitivity to tildacerfont or other CRF_1 receptor antagonist.
3. History of bilateral adrenalectomy or hypopituitarism.
4. Current treatment with dexamethasone. Participants may be transitioned off dexamethasone prior to Screening at the Investigator's discretion.
5. A clinically significant unstable medical condition, medically significant illness, or chronic disease (other than CAH) within 30 days, including but not limited to:
   a. Malignancy or <3 years of remission, except successfully treated localized skin cancer
   b. Estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m^2 (per the creatinine-based Schwartz equation)

c. Current or history of liver disease (with the exception of Gilbert's syndrome). Resolved/cured viral hepatitis may be allowed with MM approval

d. History of alcohol or substance abuse within the last year, or otherwise that would likely prevent the participant from reliably or safely participating in the study, per Investigator judgement

e. HIV at Screening

f. Any other condition that would impact participant safety or confound interpretation of study results, in the opinion of the Investigator or MM.

6. Psychiatric conditions, including but not limited to major depression, bipolar disorder, schizophrenia, or schizoaffective disorders that are not effectively controlled on medication and may have an adverse impact on study compliance. Exclusionary symptoms include hallucinations, delusions, and psychosis. Baseline values for depression and anxiety questionnaires are not exclusionary but may inform exclusion of a participant based on Exclusion Criterion 5.
7. Clinically significant abnormal clinical laboratory or ECG results during Screening. Abnormal results requiring review and discussion with the MM to discern eligibility include, but are not limited to:
   a. Any clinically meaningful abnormal ECG results, including QTcF >450 ms (males) or >460 ms (females)
   b. Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
   c. Total bilirubin >1.5x ULN (except if due to Gilbert's syndrome).
8. Females who are pregnant or nursing.
9. Use of any other investigational drug (other than tildacerfont) or device within 30 days or 5 half-lives (whichever is longer) prior to Screening through the end of the study (EOS). Prior exposure to tildacerfont is allowed, but tildacerfont should be discontinued for at least 2 weeks prior to randomization. The screening window may serve as the washout period.
10. Use of the following drugs from 30 days or 5 half-lives (whichever is longer) before Screening through the EOS (see Appendix 3):
    a. Rosiglitazone, testosterone, growth hormone, or any other medication or supplement that could impact participant safety or confound interpretation of study results
    b. Moderate to strong inhibitors and/or inducers of CYP3A4
    c. Sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 (except hormonal contraception containing $\leq$20 mcg ethinyl estradiol)
    d. 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).
11. Donation or receipt of blood from 90 days before Screening through the EOS; donation or receipt of platelets, white blood cells, or plasma from 30 days before Screening through the EOS.
12. Any known or anticipated swallowing difficulty or dysphagia during Screening or the duration of the study.

4.2. Lifestyle Considerations

4.2.1. Meals and Dietary Restrictions

Study drug can be consumed whole or crushed and sprinkled on food. For administration at home, study drug should be taken with food. Study drug may be consumed up to 30 minutes after food, if necessary. If a participant has not consumed study drug within 30 minutes after food, the participant should consume study drug with a snack.

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

4.2.2. Activity

Participants must 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.

4.2.3. Contraception Guidelines

4.2.3.1. Contraception Guidelines for Male Participants

Males capable of reproduction 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. 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 progesterone) associated with inhibition of ovulation: oral, intravaginal, or transdermal
    b. Progesterone-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
    c. Intrauterine device (IUD)
    d. Intrauterine system (IUS)
    e. Bilateral tubal occlusion.

4.2.3.2. Contraception Guidelines for Female Participants

Females of childbearing potential 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 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.
2. Must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified timepoints. 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 progesterone) associated with inhibition of ovulation: oral, intravaginal, or transdermal. Any hormonal contraception containing ethinyl estradiol must contain <20 mcg ethinyl estradiol.
b. Progesterone-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
c. IUD
d. IUS.

4.3. Screen Failures

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

Individuals who do not meet the following criteria for participation in the study may be rescreened according to the following guideline (Note: The Investigator will first consult with the MM regarding such individuals):

1. Individuals on incompatible or excluded concomitant medications may be rescreened after an appropriate washout period (e.g., 30 days or 5 half-lives, whichever is longer).
2. Individuals who have an exclusionary laboratory value during the Screening Period may be retested before the start of the Treatment Period if the Investigator believes that the prior laboratory value is not consistent with the individual's overall clinical picture.

5. STUDY TREATMENT

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

5.1. Treatment Administration

Participants will be treated with oral tildacerfont QD for 12 weeks (Cohorts 1 to 3) or BID for 4 weeks (Cohorts 4 to 9).

Pediatric age and weight-based tildacerfont dose levels are defined in Table 2. For each dose level, the amount of study drug that a participant will receive will depend on the participant's age and body weight at Screening according to Table 2.

Cohort 1 will be dosed at the equivalent of the adult 50 mg dose. Cohort 2 will receive the equivalent of the adult dose of 200 mg. If needed based on a safety concern in participants in Cohort 1, an interim dose Cohort 1a may be included. Cohort 3 will dose no higher than Cohort 2 (or Cohort 1a) but enroll up to approximately 10 participants in the younger age group of 2- to 10- years.

Cohorts 4, 6, and 7 will dose at the 200 mg adult dose equivalent BID; and Cohort 5, 8 and 9 will dose at up to 400 mg adult dose equivalent twice per day. Based on DMC recommendation and Sponsor decision, taking into account all available safety and exposure data, Cohorts 5, 8 and 9 may be initiated at 300mg adult equivalent BID for approximately 5 participants each, and then another approximately 5 may be enrolled in each at 400mg adult equivalent BID after DMC review.

Table 2. Tildacerfont Dose Levels and Pediatric Weight-Based Dosing

Weight at Screening (kg)	50 mg QD adult equivalent dose	100 mg QD adult equivalent dose	200 mg QD or BID adult equivalent dose	300mg BID adult equivalent dose	400 mg BID adult equivalent dose
Age group: 2- to 5-years					
13 to 14.1	25	50	75	100	150
14.1 to <21.2	25	50	75	100	150
21.2 to <26.1	25	50	100	150	200
26.1 to <31.8	25	75	100	150	200
31.8 to <33.9	25	75	150	150	300
≥33.9	50	100	150	150	300
Age group: 6- to 10-years					
20 to <23.7	25	50	75	100	150
23.7 to <29.9	25	50	100	150	200
29.9 to <35.5	25	75	100	150	200
35.5 to <39.2	25	75	150	200	300
39.2 to <47.5	50	100	150	200	300
≥47.5	50	100	200	300	400
Age group: 11- to 17-years					
26 to <30.5	25	50	75	100	150
30.5 to <39.2	25	50	100	150	200
39.2 to <45.7	25	75	100	150	200
45.7 to <53.4	25	75	150	200	300
53.4 to <61	50	100	150	200	300
≥61	50	100	200	300	400

Abbreviations: QD=once daily.

5.2. Preparation/Handling/Storage/Accountability

5.2.1. Acquisition and Accountability

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

5.2.2. Formulation, Appearance, Packaging, and Labeling

Tildacerfont will be provided in bottles of 25 mg, 50 mg and 200 mg tablets. Each bottle will be labeled with the product name, strength, lot number, recommended storage conditions, name of the Sponsor, and an Investigational Use Statement (e.g., “Caution: New Drug – Limited by Federal [USA] Law to Investigational Use”). Labeling will comply with all legal requirements and supply no information about individual participants.

5.2.3. Product Storage

Study drug should be stored at room temperature. Study drug 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 prior to dispensation to the participant. For additional information on product storage, please refer to the Pharmacy Manual.

5.2.4. Preparation and Administration

Participants will be taking between 1 and 6 tablets daily, depending on the dose and Cohort assignment. Participants can either swallow the tablet[s] whole or crush the tablet[s] and sprinkle on soft foods.

Cohorts 1 to 3 will receive doses QD. The dose will be taken with the evening meal. The first 2 weeks in Cohorts 1, 1a, and 2 will require dosing with a morning meal.

Cohorts 4-9 will receive BID dosing. Each dose should be taken with the morning and evening meal.

If necessary, the study drug may be taken up to 30 minutes after completing the meal(s) at home. If a participant has not consumed study drug within 30 minutes following the meal(s), the participant should consume study drug with a snack. Study drug will be dispensed at Day 1 for the duration of the study.

The Day 1 and Day 14 morning doses of tildacerfont will be administered in the clinic for Cohorts 1, 2, 4, 5, 6, 7, 8, and 9 (and 1a, if indicated) and Day 1 only for Cohort 3. Any remaining study drug will be returned for accountability at Visit 6 (Week 12) for Cohorts 1 to 3 and Visit 4 (Week 4) for Cohorts 4 to 9, any early termination (ET) Visits, and during extension visits. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol.

Preparation and administration instructions are included in the Pharmacy Manual.

5.3. Concomitant Therapy

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

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

All concomitant medications should be compared against the list of prohibited medications and the list of other medications of concern provided in Appendix 3. Participants/guardians 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 MM should be contacted if there are any questions regarding concomitant or prior therapy.

5.3.1. Glucocorticoid Replacement Therapy

5.3.1.1. General Procedures for Glucocorticoids

Concomitant medications include GCs. Information to be collected at Screening about a participant's current and prior GC therapy for the past month include the type(s) of GC, the regimen(s), and any GC stress dosing during the past month.

To be eligible for this study, participants must be on a stable dose of GC replacement for ≥1 month before Screening without evidence of non-adherence (standard of care weight-based dose adjustments

and stress dosing are allowed). Participants with the salt-wasting form of CAH who take mineralocorticoids must also be on a stable dose of mineralocorticoid replacement for ≥1 month before Screening.

On the mornings of all study visits, including the Screening Visit, participants should delay taking any morning dose of GC medication. On Day 1 all participants will receive a supervised tildacerfont dose in clinic and can take their morning GC dose at that time (after the pre-dose assessments). The same applies to Cohorts 1, 2, 4, 5, 6,7, 8, and 9 (and 1aif indicated) for Day 14. On all other visits, participants can take their morning GC dose after completion of the 8 AM (± 1 hour) assessments (PK, PD, and safety). On all other non-clinic visit days during the study, participants 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.

5.3.1.2. A4-Based Glucocorticoid Dose Adjustment Algorithm

In all cohorts, GC dose (frequency, distribution of doses, or total daily dose) may be adjusted based on A4 levels at Weeks 4 (all participants Cohorts 1 to 3; and participants in Cohorts 4 to 9 if continuing in the extension) and 8 (all participants in Cohorts 1 to 3), and Week 12 (participants in Cohorts 1 to 3 if continuing in the extension period). In the extension, GC dose may be adjusted based on A4 levels at each visit. See the Pharmacy Manual for further guidance on GC dose adjustments.

The below A4-based algorithm will be used to guide changes to GC replacement therapy. Reductions below physiologic levels should be discussed with the MM.

A4 Level ≤1x ULN

- Reduce GC dose

A4 Level 1.0 to ≤1.5x ULN

- Maintain GC dose

A4 Level >1.5x ULN

- Increase GC dose

The Sponsor or designee may contact the site after Weeks 4, 8, and 12 (or any extension visit) to confirm GC dose adjustments (note: only Week 4 for Cohorts 4 to 9). The Investigator should contact the MM if the Investigator does not intend to follow A4-based GC dose adjustment algorithm at a visit.

If a change in GC is warranted by the A4 algorithm, sites will contact participants by telephone after receipt of results (within approximately 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 participant.

5.3.1.3. Stress Dosing of Glucocorticoids

During times of clinically significant physical stress such as intercurrent illness with fever, surgical procedures, or significant trauma, participants may take extra GC consistent with the “sick day guidelines” for prevention of adrenal crisis shown in Table 3 (Bornstein 2016). The stress doses suggested in Table 3 are based on published, clinical best practice. However, management of stress dosing of GCs is ultimately at the discretion of the Investigator and/or inpatient managing physician (if hospitalized). The GCs received during a stress dosing period during the study will be captured as concomitant medications while the stress itself should be captured as an AE.

If stress dosing occurs, the MM should be consulted on how this will affect the study visit schedule and continued participation in the study.

Table 3. Sick Day Guidelines for Stress Dosing of Glucocorticoids

Condition	Stress Dosing
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 (e.g., 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). 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 50 mg/m^2 IM (approximately 50 mg HC for school-age children, 100 mg HC for adolescents)
Minor to moderate surgical stress	• HC 50 mg/m^2 IM or double or triple the routine oral GC dose (usually 1 to 2 days)
Major surgery with general anesthesia, trauma, or disease that requires intensive care	• HC 50 mg/m^2 IV, followed by HC 50 to 100 mg/m^2 per day divided every 6 hours • 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	• Rapid bolus of normal saline (0.9%) 20 mL/kg. Can repeat up to a total of 60 mL/kg within 1 hour for shock • HC 50 to 100 mg/m^2 bolus, followed by HC 50 to 100 mg/m^2 per day divided every 6 hours • 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. Alternatively, 5 to 10 mL/kg of D10W for children <12 years of age • Cardiac monitoring: rapid tapering and switch to oral regimen depending on clinical state

Abbreviations: D10W=dextrose 10%; D25W=dextrose 25%; GC=glucocorticoid; HC=hydrocortisone; IM=intramuscular; IV=intravenous.

To prevent hypoglycemia, the participant should drink small amounts of clear sugar-containing liquids frequently and/or consume carbohydrates if the participant is able, glucose monitoring should be considered, and IV sodium and glucose replacement may be required (Clayton 2002, Merke and Bornstein 2005, Han 2014).

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

Participants will maintain stress dosing until symptoms subside (or according to the clinical judgment of the treating physician), then return to his/her usual GC regimen.

5.3.2. Prohibited Concomitant Medications

- Use of other investigational drugs and devices are prohibited during the study.
- Rosiglitazone, testosterone, growth hormone, or any other medication or supplement that could impact participant safety or confound interpretation of study results are prohibited.

- Moderate to strong inhibitors and/or inducers of cytochrome P450 3A4 (CYP3A4); this includes consumption of grapefruit, grapefruit juice, or any foods that are known to be strong CYP3A4 inhibitors from 1 day before the first dose of study drug until after the final dose.
- Sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 (e.g., dexamethasone and oxycodone)

  Note: This does NOT apply to hormonal contraception containing ≤20 mcg ethinyl estradiol.
- 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)

Appendix 5 provides a non-exhaustive list of medications, including many commonly used medications, which are prohibited because of their potential for metabolic interactions with tildacerfont. It is critical that each participant's concomitant medications are carefully compared to the list in Appendix 5.

6. STUDY DRUG DISCONTINUATION AND PARTICIPANT WITHDRAWAL

6.1. Study Drug Discontinuation

Participants and/or their parent/guardian may voluntarily discontinue study drug at any time. The Investigator and/or Sponsor may also discontinue a participant's study drug at any time. When feasible, Investigators should discuss any safety concerns with the MM as soon as possible to determine whether a participant should continue or discontinue study drug. Study drug will be discontinued in participants who experience individual treatment-stopping criteria described within this section. The Sponsor and Investigator will make efforts (when possible) to continue to collect data on participants who discontinue study drug.

If study drug is discontinued, the Investigator will report the discontinuation to the MM, document the date and reason for study drug discontinuation on the appropriate electronic case report form (eCRF), schedule an ET visit for the participant (see the Schedule of Activities in Appendix 1, Appendix 2, Appendix 3, and Appendix 4) provide or arrange for appropriate follow-up, and document the course of the participant's condition.

Participants who prematurely discontinue study drug may be replaced at the discretion of the Sponsor to ensure adequate numbers of evaluable participants.

6.1.1. Dose-Limiting Toxicity Stopping Criteria

A DLT is defined as a Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher treatment-emergent adverse event (TEAE) considered at least possibly related to study drug. If a participant experiences a DLT, study drug will be discontinued. DLTs are clinically significant AEs (see Section 6.1.7).

6.1.2. Safety Monitoring and Stopping Rules for Abnormal Liver Chemistry Measurements

The following was adapted in accordance with the non-binding recommendations contained within the FDA Guidance for Industry Drug-Induced Liver Injury: Pre-marketing Clinical Evaluation, from the U.S. Department of Health and Human Services in July 2009.

Special attention is paid to potential liver toxicity because tildacerfont was identified as a bile salt export pump (BSEP) inhibitor based on pre-clinical studies. Although in vitro BSEP inhibition does not reliably predict in vivo BSEP inhibition, Spruce believes that the pre-clinical findings warrant ongoing clinical monitoring (Jonathan 2018). Consequently, abnormal transaminase results will be assessed as follows.

If stopping criteria are met at any time during the Treatment Period, study drug should be held until confirmatory testing of the transaminase, with additional measurements of total bilirubin, alkaline phosphatase (ALP), complete blood count (CBC) with differential and international normalized ratio (INR), is performed. Ideally, confirmatory testing would be performed within 48 hours of the initial receipt of the abnormal result. Confirmation testing through the central lab is preferred, but local laboratory testing may be necessary in certain circumstances. Confirmed cases meeting stopping criteria will be reported as an AESI and in cases where a possible Hy's Law case is present, the event should also be reported as an SAE. Table 4 outlines specific stopping criteria for this study.

Table 4. Stopping Criteria and Increased Monitoring for Liver Chemistry Elevations

Criteria		Actions
Participant has symptoms (new or worsening) believed to be related to liver injury or hypersensitivity[1]		Hold study drug, measure liver chemistry (AST/ALT/ALP), CBC with differential, total bilirubin, total bile acids and INR as soon as possible and notify Sponsor.
ALT 3x ULN		Discontinue study drug and notify Sponsor.
ALT 3x ULN	**AND** total bilirubin 2x ULN (>35% direct bilirubin)[2]	Discontinue study drug and notify Sponsor. Possible Hy's Law case—**report as an AESI and SAE**.
	AND INR >1.5	Discontinue study drug and notify Sponsor. Possible Hy's Law case—**report as an AESI and SAE**.
Total Bile Acids >5xULN		Discontinue study drug and notify Sponsor.

Abbreviations: AESI=adverse event of special interest; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=Complete Blood Count, INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal.

[1] 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. Due to similarities in symptoms with adrenal insufficiency, clinical judgement will be required to assess likelihood that symptoms may be hepatic in origin.

[2] 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.

Investigation of the underlying cause of these transaminase elevations should include, but is not limited to:

- A detailed history of symptoms as well as current and prior medical diseases, especially biliary tract disease, co-morbid conditions associated with development of nonalcoholic steatohepatitis, and cardiovascular disease that would compromise adequate blood supply to the liver
- Examination of concomitant drug use (inclusive of OTC, herbal/dietary supplements, alcohol and recreational drug use)
- Environmental and chemical exposures
- Serology testing, as appropriate, based on laboratory findings, clinical exam and exposure history (i.e., viral hepatitis, Epstein Barr virus)
- Additional investigations as appropriate such as gastrointestinal (GI)/hepatology consultation, imaging studies or other laboratory testing may be performed at the discretion of the Investigator, in consultation with the Sponsor MM.

6.1.3. Laboratory Monitoring of Liver Function

- Monitor liver enzymes, total bilirubin, total bile acids, and INR at least two times a week until transaminase levels are <3x ULN, total bile acids are <5x ULN, total bilirubin <2xULN, and INR ≤1.5x ULN or levels stabilize, and the participant is asymptomatic.
- Obtain additional tests to evaluate liver function, such as fractionated bilirubin, as deemed appropriate.

- Thereafter, repeat testing will be performed as appropriate for the clinical circumstance until resolution or stability of transaminase values, total bilirubin, total bile acids and INR is achieved and any symptoms, if present, have abated.

In the event that study drug is discontinued, the decision to rechallenge will be made on a case-by-case basis and will require written approval by the Sponsor.

6.1.4. QT Stopping Criteria

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

- QTcF >500 msec OR uncorrected QT >600 msec
- Change from Screening 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.

6.1.5. Suicidality Stopping Criteria

Tildacerfont is 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, participants will be monitored for such events during this study using the C-SSRS. Any participant who exhibits Suicidal Behavior or Suicidal Ideation in their responses on 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 7.2.8).

6.1.6. Depression or Anxiety Stopping Criteria

Participants will be monitored for depression and anxiety during the study using the Patient Reported Outcomes Measurement Information System (PROMIS) Pediatric SF (Short Form) v2.0, the PROMIS Parent-Proxy SF (Short Form) v2.0, or the Survey of Well-Being of Young Children (SWYC). The questionnaire used will depend upon the participant's age. Any participant who develops severe depression or anxiety (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 and if seriousness criteria are met, also reported as an SAE (e.g., requiring hospitalization) (see Section 7.2.8).

6.1.7. Clinically Significant Adverse Events

Clinically significant AEs include but are not limited to SAEs, AEs leading to study drug discontinuation/study withdrawal (e.g., based on stopping criteria in Section 6.1), DLTs (Section 6.1.1), and AESIs (Section 7.2.8). The occurrence of any clinically significant AE will be reported to the DMC on an ongoing basis.

The Investigator should consider study drug discontinuation and appropriate safety follow-up for a participant who experiences a potentially clinically significant AE. When feasible, the Investigator should contact the MM to discuss the participant's clinical condition before discontinuing study drug.

6.1.8. Dose Limiting Toxicity

If 2 participants in a cohort meet individual stopping criteria, the entire cohort will be stopped or dose-reduced.

6.2. Participant Withdrawal from the Study

Participants and/or their parent or guardian are free to withdraw from the study at any time upon request. If the participant/parent/guardian withdraws consent for disclosure of future information, the

Sponsor may retain and continue to use any data collected before the withdrawal of consent. The participant's parent or guardian may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Participants 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 participant

A participant 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 participant no longer meets eligibility criteria
- Study termination by the Sponsor

If possible, an ET visit (see Schedule of Activities in Appendix 1 and Appendix 2) should be conducted for any participant that received at least one dose of study drug before participant withdrawal. The Investigator must document the date and primary reason for the withdrawal on the appropriate eCRF. Participants who withdraw prematurely may be replaced at the discretion of the Sponsor to ensure adequate numbers of evaluable participants.

6.3. Lost to Follow-up

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

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

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

7. STUDY ASSESSMENTS AND PROCEDURES

The timing of study assessments and procedures is provided in the Schedule of Activities in Appendix 1 (Cohorts 1-3) and Appendix 3 (Cohorts 4-9). The Schedule of Activities for the extension period is provided in Appendix 2 (Cohorts 1-3) and Appendix 4 (Cohorts 4-9).

7.1. Safety Assessments

Safety assessments will include monitoring and recording all AEs (including SAEs, AEs leading to discontinuation/withdrawal, DLTs, and AESIs), physical examination, vital signs assessment, ECGs, and clinical laboratories. AE procedures are described in Section 7.2.

7.1.1. Physical Examination

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

An abbreviated/directed physical examination should include the following components: cardiovascular, respiratory, abdomen, and any other systems indicated by history or clinical judgment.

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

7.1.2. Vital Signs

Vital signs consist of systolic and diastolic blood pressure, pulse rate, respiration rate, and body temperature. The participant should ideally have an empty bladder. Vital signs will be measured as specified in the Schedule of Activities (Appendix 1 and Appendix 2) and as clinically indicated.

7.1.3. Body Weight and Height

Total body weight (actual body weight) will be measured at every visit using a calibrated balance. Height needs to be recorded at Screening only. Body mass index (BMI) and body surface area (BSA) will be calculated using these measurements.

7.1.4. 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 QTcF. Tracings may be repeated as needed until the Investigator feels the results are reliable. 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 6.1.4 for QT individual treatment-stopping criteria and any additional ECGs that may be necessary.

7.1.5. Clinical Laboratories

All visits will take place in the morning so that labs can be drawn prior to the first GC dose. Participants may arrive in time to have labs drawn at 7am (8am ± 1 hour). Fasting is not required for laboratory assessments. Clinical laboratory assessments include coagulation panel (Screening only), hematology, chemistry (including liver function tests AST, ALT, ALT, gamma-glutamyl transferase [GGT], total and direct bilirubin, and total bile acids), and thyroid panel. eGFR for Screening and throughout the trial will be calculated from blood creatinine measured as part of Screening clinical chemistry utilizing the creatinine-based Schwartz equation.

A complete list of study-required clinical laboratory tests is provided in Appendix 6.

All study-required clinical laboratory tests should be conducted in accordance with the laboratory manual and will be performed by a central laboratory. If it is not feasible to draw labs in clinic, local labs may be used to monitor safety. Local A4 levels may be used for GC dose adjustment during the extension period with Sponsor's approval.

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 participant'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 MM. 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.

7.1.6. Psychiatric Evaluations

Psychiatric evaluations may be conducted at any time during the study with changes in psychiatric status or if a concern arises; questionnaires may be administered on an as-needed basis.

7.1.6.1. 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 risk and ideation in patients participating 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 participant eligibility. The Since Last Visit Version of the C-SSRS will be used at all subsequent visits specified.

Refer to Section 6.1.5 for suicidality individual treatment-stopping criteria.

7.1.6.2. Depression Assessment

The PROMIS Pediatric SF v2.0 and the PROMIS Parent Proxy SF v2.0 will be used during the study to monitor participants for depression (Yount 2019). The PROMIS Pediatric SF v2.0 is self-administered and the PROMIS Parent Proxy SF v2.0 is completed by the parent of a child in the study, to assess for symptoms of depression. The assessment consists of 8 items using multiple choice response format and will be used at screening and all subsequent visits specified.

Refer to Section 6.1.6 for depression and/or anxiety individual treatment-stopping criteria.

7.1.6.3. Anxiety Assessment

The PROMIS Pediatric Anxiety SF v2.0 and the PROMIS Parent Proxy Anxiety SF v2.0 will be used during the study to monitor participants for anxiety. The Pediatric version is self-administered and the PROMIS Parent Proxy SF v2.0 is completed by the parent of a child in the study to assess for symptoms of anxiety. The assessment consists of 8 items using a multiple-choice response format and will be used at screening and all subsequent visits specified.

Refer to Section 6.1.6 for depression and/or anxiety individual treatment-stopping criteria.

7.1.6.4. Survey of Well-Being of Young Children

The SWYC is a brief questionnaire (completed by parents) that assesses the following 3 categories of well-being in children 2 to 4 years of age: developmental, emotional/behavioral, and family.

Refer to Section 6.1.6 for depression and/or anxiety individual treatment-stopping criteria.

7.2. Adverse Events and Serious Adverse Events

7.2.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a participant participating in a clinical trial. 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 TEAE 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:

- It is associated with accompanying symptoms
- It requires additional diagnostic testing or medical/surgical intervention
- It leads to a change in study drug dosing or study drug discontinuation, significant additional concomitant drug treatment, or other therapy
- It 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 participant's condition
- The underlying disease and its signs and symptoms, unless they are more severe than expected for the participant'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.

7.2.2. 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 participant 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 rehabilitation, hospice, or skilled nursing facilities; respite care; nursing homes; observation in an Emergency Department of Acute Care center, or 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., participant 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 participant.

7.2.3. Classification of an Adverse Event

The Investigator must record all AEs in the eCRF with information about:

- Duration (start and end dates)
- Severity (Section 7.2.3.1)
- Relationship to study drug (Section 7.2.3.2)
- Action(s) taken and, as relevant, the outcome (Section 7.2.3.3 and Section 7.2.3.4)
- Seriousness (Section 7.2.2)

7.2.3.1. 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 5.

Table 5. 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 participant'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 7.2.2, 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.

7.2.3.2. Relationship to Study Drug

The Investigator will assess the relationship of each AE to study drug according to the categories in Table 6. This assessment will serve to determine whether there exists a reasonable possibility that the study drug caused or contributed to the AE.

Table 6. Relatedness of Adverse Event to Study Drug

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

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 administration will be considered and investigated.

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

7.2.3.3. Action Taken

The action taken with the study drug in response to an AE must be classified as one of the following:

- No change (study medication schedule maintained or no action taken)
- Study medication interrupted
- Study medication discontinued.

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the participant. If medication is administered to treat the AE, this medication should be recorded.

7.2.3.4. Outcome

The outcome of each AE will be recorded as one of the categories in Table 7.

Table 7. Outcome of Adverse Events

Not recovered/not resolved: The event has not improved or recuperated.
Recovered/resolved: The event has improved or recuperated. The participant 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 participant 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 participant/guardian or the participant's records to determine the outcome (i.e., participant/guardian 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.

7.2.4. Time Period and Frequency for Event Assessment and Follow-up

AEs will be recorded from the time the informed consent form (ICF) is signed until the end of the follow-up period. AEs will be assessed at each study visit, and participants should be encouraged to contact the study site to report AEs that occur between scheduled visits. AEs that occur in the time period between informed consent and the first dose of study drug of the Treatment Period should be recorded but will not be considered TEAEs.

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event has been shown to be unrelated to study drug, or the participant is lost to follow-up (as defined in Section 6.3).

7.2.5. Adverse Event Reporting

The Investigator is to report all AEs, whether volunteered by the participant, discovered through questioning, or directly detected, that occur in the time period specified in Section 7.2.4 and according to classifications described in Section 7.2.3.

Non-serious AEs that do not require immediate reporting are to be reported on the AE eCRF. SAEs and AESIs will be reported on the SAE Report Form (see Section 7.2.6).

Clinically significant AEs such as SAEs, AEs leading to study drug discontinuation/study withdrawal (e.g., based on stopping criteria in Section 6.1), DLTs (Section 6.1.1), and AESIs (Section 7.2.8) that are considered at least possibly related to study drug will be reported to the DMC on an ongoing basis.

7.2.6. 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. AESIs (see Section 7.2.8) will also be reported in the electronic data capture (EDC) system and on the SAE Report Form 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 participant 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 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 FDA) and to all Institutional Review Boards (IRBs)/Ethics Committees (ECs) overseeing the conduct of the study, in accordance with FDA 21 CFR 312.32.

7.2.7. Reporting of Pregnancy

Any participant who becomes pregnant during the study will have study drug discontinued immediately and be withdrawn from the study. All pregnancies in female participants or in the female partners of male participants 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 participant who becomes pregnant while participating in this study, the Investigator will collect information about the pregnancy and follow up with the participant to determine the outcome of the pregnancy and the status of mother and child.

Male participants will be instructed to notify the site in the event that any female partner becomes pregnant. If any female partner of a male participant who received at least 1 dose of study drug becomes pregnant within 90 days of the male participant'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 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 participants, he or she may learn of such an SAE through spontaneous reporting.

7.2.8. Adverse Events of Special Interest

AESIs are those AEs (independent of seriousness criteria) that are of specific concern to this study and for which ongoing monitoring and communication with the Investigator and Sponsor may be appropriate. These events will be reported on the SAE Report Form, 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 6.1.2). Cases of Hy's Law should be reported as an AESI and SAE.
- Suicidality as indicated by responses on the C-SSRS (see Section 6.1.5 regarding study stopping criteria).
- Depression or anxiety that is moderate or severe (CTCAE Grade 2 or higher), as assessed by the Investigator (see Section 6.1.6 regarding study drug stopping criteria for depression or anxiety). This will be reported as an AESI and if seriousness criteria are met, reported as an SAE.
- Adverse events of adrenal insufficiency are considered AESIs and will be reported on a separate Adrenal Insufficiency Form. Additionally, symptoms of adrenal insufficiency will be reported as SAE if they necessitate parenteral GC administration by a health care professional and two of the following criteria occur or are met: hypotension (systolic blood pressure <90 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, or 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 the health care provider, emergency facility or hospital 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 parenteral GC was administered and the duration of administration?
        - What concomitant medications were administered?
        - What clinical laboratory results are available?
        - What AEs occurred?
        - What was the duration of stay if admitted to the hospital?
        - What was deemed to be the inciting factor leading to adrenal crisis?

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

Adverse events or other conditions that lead to GC stress dosing should not be reported as AEs of adrenal insufficiency since the stress dosing is done to prevent, not treat, adrenal insufficiency. If an AE, such as an infection, results in GC stress dosing, the AE should be captured in the Adverse Event CRF. The following additional information will be collected in the patient diary during episodes of GC stress

dosing: start and stop date, concomitant medications, cause for stress dosing (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.

7.3. Pharmacokinetic and Pharmacodynamic Assessments

A summary of blood draws for assessment of tildacerfont concentration and PD is presented in Table 8.

Table 8. Tildacerfont Concentration and PD Sampling Time Points

Sample	Day 1	Week 2	Week 4	Week 8	Week 12	ET	F/U	EP (all visits)
PD markers (ACTH, 17-OHP, A4, testosterone, and 11KT)	Cohorts 1, 2, 4, 5, 6, & 7 (8 & 9 if indicated) Pre-dose[1] 0.5-1.5 hr post-dose 3-5 hr post dose Cohort 3 Single sample[1]	Cohorts 1, 2, 4, 5, 6, & 7 (8 & 9 if indicated) Pre-dose[1] 0.5-1.5 hr post-dose 3-5 hr post dose Cohort 3 Single sample[1]	Cohorts 1, 2, 4, 5, 6, & 7 (8 & 9 if indicated) Single sample[1]	Cohorts 1, 2, & 3 (1a if indicated) Single sample[1]	Cohorts 1, 2, & 3 (1a if indicated) Single sample[1]	All Cohorts Single sample[1]	X[2]	All Participants Single sample[1]
Tildacerfont concentrations	Cohorts 1, 2, 4, 5, 6, & 7 (8 & 9 if indicated) Pre-dose[1] 0.5-1.5 hr post-dose 3-5 hr post dose Cohort 3 Single sample[1]	Cohorts 1, 2, 4, 5, 6, & 7 (8 & 9 if indicated) Pre-dose[1] 0.5-1.5 hr post-dose 3-5 hr post dose Cohort 3 Single sample[1]	Cohorts 1, 2, 4, 5, 6, & 7 (8 & 9 if indicated) Single sample[1]	Cohorts 1, 2, & 3 (1a if indicated) Single sample[1]	Cohorts 1, 2, & 3 (1a if indicated) Single sample[1]	All Cohorts Single sample[1]	X[2]	All Participants Single sample[1]

Abbreviations: 11KT = 11-ketotestosterone, 17-OHP= 17-hydroxyprogesterone; A4 = androstenedione; ACTH=adrenocorticotropic hormone, corticotropin; F/U = follow-up; GC = glucocorticoid; EP= extension period; PD=pharmacodynamics.

[1] These samples will be collected at approximately 8 AM (± 1 hour) before participants take any morning dose of GC (except for Cohorts 4 to 9, where sample will be collected prior to the tildacerfont morning dose and GC dose) and do not require fasting.

[2] As needed based upon abnormalities in prior visits.

Concentration of tildacerfont will be measured by a bioanalytical laboratory using validated methods. Detailed instructions for the collection and handling of biological samples will be provided separately in the Laboratory Manual.

8. STATISTICAL CONSIDERATIONS

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

8.1. Sample Size Determination

A sample size of up to approximately 70 participants (i.e., 15 adults, 30 children 11- to 17-years of age, and 25 children 2- to 10-years), will provide adequate data to assess the initial safety of tildacerfont in a pediatric and adult population and provide data to support the continued use of the PBPK model to determine pediatric dosing requirements in future studies.

8.2. Populations for Analyses

The Safety Population will include all participants who receive at least 1 dose of study drug and will be the primary analysis set for general and safety analyses.

The PK Population will include all participants in the Safety Population with at least 1 post-dose sample above the limit of quantification.

The PD Population will include all participants in the Safety Population with at least 1 evaluable post-baseline PD assessment.

8.3. Statistical Analyses

8.3.1. 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).

All continuous variables will be presented using an 8-point descriptive summary (n, mean, standard deviation, median, interquartile range [25th percentile, 75th percentile], minimum, and maximum) by dose, as available. Categorical variables will be summarized by frequency and by percentage of participants in corresponding categories.

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

8.3.2. Demographics and Baseline Characteristics

Listings and summaries will be provided for demographics (age, sex, ethnicity, and race) and baseline characteristics (weight, height, BMI, and BSA) for the Safety Population.

Baseline biomarkers and GC regimen will be summarized for the Safety Population.

8.3.3. Concomitant Medications

Prescription, OTC, and alternative medication use will be listed.

8.3.4. Safety Analyses

The Safety Population will be used for all safety analyses. Safety data will be listed by participant and summarized by adult equivalent dose levels (50, 100, 200 mg QD; and 200 mg, possibly 300 and/or 400 mg BID) using the frequency of event or descriptive statistical summaries, as appropriate. Listings and summary tables will be provided for AEs, clinical laboratory tests, vital signs, and ECG data. Urinalysis, psychiatric evaluations, concomitant medications, and physical examinations will be presented in listings only.

A DMC will review accumulating safety information by cohort. Refer to Section 9.4.4 for information on the DMC.

8.3.4.1. Extent of Exposure

Dosing information for individual participants will be listed and include nominal dose (mg) and dose adjusted for body weight (mg/kg). Using dosing data, estimates of exposure to tildacerfont will be summarized. Dose discontinuations and reasons for study drug discontinuation will be listed and summarized.

8.3.4.2. 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 participants reporting each observed event.

AEs that occur before the first dose of study drug of the Treatment Period will be distinguished from TEAEs (defined in Section 7.2.1). All AEs, AESIs and TEAEs will be listed by participant. The frequency of participants who experience TEAEs will be summarized overall and by cohort. TEAEs will also be summarized by relationship to study drug and severity.

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

8.3.4.3. Clinical Laboratory Data

Clinical laboratory test results will be listed by participant. 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.

8.3.4.4. 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.

8.3.4.5. Electrocardiogram Data

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

8.3.5. Pharmacokinetic Analyses

Tildacerfont concentration data will be listed by participant. Validation and refinement of the PBPK model using concentration data will be described in a separate pharmacometrics analysis plan.

8.3.6. Pharmacodynamic Analyses

The PD Population will be used for all PD analyses.

Change from baseline in PD biomarkers, ACTH, 17-OHP, A4, testosterone, and 11KT will be summarized descriptively using the 8-point summary as well as geometric mean ratios comparing baseline to post baseline, as appropriate. T will be summarized separately for males and females.

Change from baseline in select PD ratios will also be summarized, A4/T (males only) and 11KT/T (males and females, separately). Other ratios may be identified in the statistical analysis plan.

The proportion of participants with a reduction in biomarkers at Weeks 4 (all cohorts) and 12 (Cohorts 1 to 3 only) will be summarized descriptively, including by subgroup, baseline A4 ≤ULN, Baseline A4 >ULN:

- Any reduction
- ≥50% reduction
- A4 ≤ULN

Change from baseline in GC total daily dose at Week 12 and during the extension period will be summarized descriptively:

- Absolute change (mg)
- Absolute change adjusted for body surface area (mg/m^2)
- Percent change (%)
- Proportion of participants with GC reduction
- Proportion of participants with baseline dosing >3x daily who decrease frequency of administration ≤3x daily

The proportion of participant with a ≥1 mg/m^2 GC reduction or any reduction from baseline in A4 at Week 12 will be summarized descriptively.

Changes in adrenal biomarkers and GC will be summarized in a similar manner for the extension period.

8.3.7. Psychiatric Evaluation Analyses

The psychiatric evaluation analysis will be conducted on the Safety Population. Assessments of suicidality, depression, and anxiety will be listed.

9. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1. Informed Consent

For each study participant, written informed consent/assent must be obtained before the participant may be enrolled into the study and before any protocol-specified procedures may be conducted. In the case of pediatric participants (<18 years old) in this study, the participant's legal guardian will sign and date the ICF (which will be witnessed, where required by law or regulation), and a pediatric participant who is capable will sign and date a separate assent document. Emancipated or mature minors may give autonomous consent, as permitted by institutional requirements and local laws. The ICF will also be signed and dated by the Investigator and/or designee. The process of obtaining informed consent/assent should be documented in the participant source documents. Each participant/guardian will be provided a copy of the signed and dated ICF/assent form. For participants who continue in the extension period, a separate ICF/assent form is required.

As part of the informed consent/assent process, the Investigator or designee must explain to each participant/guardian the purpose and procedures of the study and the possible risks involved. Participants/guardians 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/assent form and any other materials provided to participants/guardians or investigative staff must use vocabulary and language that can be readily understood.

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

9.2. Study Discontinuation and Closure

Premature study termination may occur because of a regulatory authority decision, change in opinion of the IRB, 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 participant 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 participants within 7 days and have them complete final visit safety assessments. As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

9.3. 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 participant's privacy is maintained. The Sponsor will assign each participant a unique identifier. Any

participant records or datasets that are transferred from the site to the Sponsor will contain this identifier only; participant names or any information that would make the participant identifiable will not be transferred.

9.4. Key Roles and Study Governance

9.4.1. 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, Good Clinical Practice (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.

9.4.2. 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.

9.4.3. Institutional Review Board

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

9.4.4. Data Monitoring Committee

An independent DMC consisting of external experts not associated with this study will be established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study and to approve cohort progression.

DMC responsibilities are further described in the DMC charter.

9.5. Clinical Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative or designee will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will regularly check the completeness of participant 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 10.4 for information on monitoring visits in the context of coronavirus disease 2019 (COVID-19).

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/assent, 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 eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of participants will be disclosed.

Refer to Section 9.7.1 for information on eCRFs and source documents.

9.6. 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.

9.7. Data Handling and Record Keeping

9.7.1. Data Collection and Management Responsibilities

An eCRF must be completed for each enrolled participant. Completed original eCRFs 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. Electronic CRFs 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 participant in the study, the Investigator must maintain source documents at the trial site consisting of the original assent form/ICF signed by the participant/guardian (a copy of which is given to the participant/guardian), the hospital/clinic or physician medical records/chart for the participant, 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 participant'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.

9.7.2. 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 participants (sufficient information to link records [e.g., eCRFs and hospital records]), all original signed ICFs/assent forms, 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.

9.8. Protocol Deviations

If a protocol deviation occurs that affects a participant'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 review and approval/favorable opinion (see Section 9.10), the deviation will be reported as soon as possible to 1) the IRB 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) must be sent to the Sponsor.
Protocol deviations will be included in the Clinical Study Report.

9.9. 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.

9.10. 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, except where necessary to eliminate an immediate hazard(s) to study participants. Any significant protocol deviation must be documented (see Section 9.8).

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

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

10. RISK MITIGATION DURING THE CLINICAL TRIAL

10.1. Risk/Benefit Assessment in the Context of COVID-19 or Other Obstacles

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 patients with CAH if they are not managed appropriately. The emergence of diseases such as COVID-19 increases the overall infection risk in affected communities, including patients with CAH who reside in those communities.

Participation in a clinical trial provides participants with increased access to healthcare resources and reinforcement of appropriate practices during a time of increased infection risk. Study participants will have access to healthcare professionals on a more intensive schedule than in normal clinical practice for the management of CAH. The standard of care for a CAH patient with an infection or febrile illness is to increase the patient's GC dose to accommodate the additional stress and prevent an adrenal crisis (see Section 5.3.1.3).

10.2. Study Conduct in the Context of COVID-19 or Other Obstacles

If a clinic visit is not possible because of COVID-19 restrictions, or other unforeseen obstacles, they will not be conducted. A telemedicine visit may be conducted as an alternative to an on-site clinic visit. Local labs may be used. A GC dose reduction based on the local A4 may be allowed with Sponsor approval.

10.3. Participant Disposition in the Context of COVID-19 or Other Obstacles

If a participant develops an active COVID-19 infection (whether confirmed or suspected), or another such disease during the course of the study, the Investigator will work with the participant/guardian and the MM to determine the best course of action, taking into consideration the AE and SAE guidelines in Section 7.2 and the individual stopping criteria for clinically significant AEs in Section 6.1.7. If study drug is discontinued or a participant is withdrawn from the study because of COVID-19 or another such disease, the reason for ET will be captured in the EDC system as such.

10.4. Regulatory and Study Oversight Considerations in the Context of COVID-19 or Other Obstacles

If planned onsite monitoring visits are not possible because of COVID-19, other unforeseen obstacles, remote monitoring may occur, if allowed by local and federal legal and regulatory requirements. If a protocol deviation is the result of COVID-19–related or other such circumstances, this information should be captured.

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12. APPENDICES

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APPENDIX 1. SCHEDULE OF ACTIVITIES FOR COHORTS 1, 1A, 2, AND 3

	Screening[1]	Treatment Period					Early Termination	Safety Follow-up[2]
		Day 1	Week 2	Week 4	Week 8	Week 12 (EOT)		
VISIT NUMBER	**1**	**2**	**3**	**4**	**5**	**6**		**7**
STUDY DAY	**≤14 days before V2**	**1**	**14**	**28**	**56**	**84**		**Last dose +30 days**
Visit windows			±3 days	±3 days	±3 days	±3 days		± 7 days
Informed consent/assent	X							
Inclusion/exclusion criteria	X	X						
Demography & medical history	X							
Review of prior medications from past year	X							
Review of concomitant medications	X	X	X	X	X	X	X	X
Hepatitis B & C and HIV Screening	X							
Pregnancy test for FOCP [3]	X	X	X	X	X	X	X	X[6]
Laboratory assessments [4, 5]	X	X	X	X	X	X	X	X[6]
Pharmacodynamics and Tildacerfont Concentration Samples (by Cohort)								
Cohorts 1 & 2 PD markers and tildacerfont concentration (serial, drawn together) [7] (also 1a if indicated)		X	X					
Cohorts 1 & 2 PD markers (single sample)[8] (also 1a if indicated)				X	X	X	X	X[6]
Cohorts 1 & 2 tildacerfont concentration (single sample)[9] (also 1a if indicated)				X	X	X	X	X[6]
Cohort 3 PD markers (single sample)[8]		X	X	X	X	X	X	X[6]
Cohort 3 tildacerfont concentration (single sample)[9]		X	X	X	X	X	X	X[6]
A4-based GC dose adjustment[10]				X	X	X		
Weight-based tildacerfont dose adjustment	X					X		
Urinalysis [11]	X		X			X	X	X[6]

	Screening[1]	Treatment Period					Early Termination	Safety Follow-up[2]
		Day 1	Week 2	Week 4	Week 8	Week 12 (EOT)		
VISIT NUMBER	**1**	**2**	**3**	**4**	**5**	**6**		**7**
STUDY DAY	**≤14 days before V2**	**1**	**14**	**28**	**56**	**84**		**Last dose +30 days**
Visit windows			±3 days	±3 days	±3 days	±3 days		± 7 days
Vital signs [12], body weight	X	X	X	X	X	X	X	X[6]
Physical exam [13]	X	X	X	X	X	X	X	X[6]
12-lead ECG	X		X[14]			X	X	X[6]
Bone age and predicted adult height[15]	X							
C-SSRS [16]	X		X	X	X	X	X	X[6]
PROMIS [17]	X		X	X	X	X	X	X[6]
SWYC[18]	X		X	X	X	X	X	X[6]
Dispense study drug[19]		X						
Study drug accountability			X	X	X	X	X	
Clinic drug administration [20]		X	X					
Review any AEs		X	X	X	X	X	X	X

Abbreviations: 11KT=11-ketotestosterone; A4=androstenedione; ACTH=adrenocorticotropin hormone; AEs=adverse events; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; CRO=contract research organization; C-SSRS= Columbia–Suicide Severity Rating Scale; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOT=end of treatment; ET=early termination; FOCP=female of childbearing potential; GC=glucocorticoid; GGT=gamma-glutamyl transferase; HIV=human immunodeficiency virus; EP=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; PROMIS=Patient Reported Outcomes Measurement Information System; 17-OHP=17-hydroxyprogesterone; SWYC=Survey of Well-being of Young Children; T=testosterone.

[1] The Screening Period may be extended as approved by the Sponsor or CRO designee.

[2] For participants continuing in the EP period, the Safety Follow-up Visit will be 30 days after their last dose in the EP Period.

[3] A pregnancy test will be performed at every visit for FOCP. The Screening Visit will include a serum pregnancy test. All subsequent visits will include urine pregnancy tests. Any positive urine pregnancy test must be followed up by a serum pregnancy test for confirmation.

[4] Labs will be drawn at approximately 8 AM (±1 h) before any morning dose of GC medication.

[5] Laboratory assessments include: coagulation panel (Screening only), hematology, chemistry (including liver function tests AST, ALT, ALP, GGT, total and direct bilirubin, and total bile acids), thyroid panel. Fasting is not required.

[6] As needed based upon safety concerns, per Investigator discretion.

[7] For Cohorts 1 and 2, serial blood samples at 3 timepoints to assess PD (ACTH, 17-OHP, A4, testosterone and 11KT) cortisol and tildacerfont concentrations: pre-dose (prior to GC dosing and tildacerfont dosing), 0.5 to 1.5 hours post GC and tildacerfont dose, and 3 to 5 hours post-GC and tildacerfont dose.

[8] PD Samples (ACTH, 17-OHP, A4, testosterone, 11KT). They must be drawn prior to GC dosing, at approximately 8 AM (± 1 h). Fasting is not required.
[9] Tildacerfont concentration collected prior to GC dosing. Fasting is not required.
[10] In all cohorts, GC dose (frequency or total daily dose) may be adjusted based on A4 levels collected at Weeks 4 and 8 (all participants) and Week 12 (for those participants continuing in the optional EP). If a change in GC is warranted by the A4 algorithm, sites will contact participants by telephone after receipt of results (within approximately 2 weeks) after each applicable study visit.
[11]Urinalysis should include the following: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, by dipstick. Microscopic examination should be obtained if blood or protein is abnormal. For visits in which tildacerfont is administered, urinalysis should be performed pre-dose.
[12] Systolic and diastolic blood pressure, pulse rate, body temperature, and respiration rate. Height will only be collected at Screening.
[13] Full physical exam is performed at Visit 2, Visit 6, and ET Visit; an abbreviated/directed physical exam is performed at all other visits.
[14] Day 1 ECGs are conducted pre-dose. Day 14 ECG is dose independent, as participants should be at steady state.
[15] Historical bone age and predicted adult height calculation may be used if performed ≤6 months prior to Screening. If no appropriate image is available, x-ray of left hand and wrist will be performed to assess bone age and calculate predicted adult height.
[16] The C-SSRS, to assess suicidality, is only conducted for participants aged 6 to 17 years.
[17] PROMIS, to assess anxiety and depression, is conducted for participants aged 5 to 17 years.
[18] The SWYC to assess anxiety and depression is only conducted in Cohort 3 participants ≤5 years of age.
[19] A 12-week supply of study drug will be dispensed at Visit 2 (Day 1). Participants should bring study drug to all visits for accountability. Upon receipt of study drug, the pharmacy will hold/store two doses to ensure that in-clinic dosing can occur at Visit 3 (Week 2) in the event a participant does not bring study drug to the visit.
[20] Cohorts 1 and 2 dosing:
Cohorts 1 and 2 (and 1a if indicated) will dose with a morning meal for the first 14 days of the study. Cohorts 1 and 2 (and 1a if indicated) will take the study drug at the clinic on Day 1 (Visit 2) (to allow for a 1-hour safety observational period and serial tildacerfont concentrations), and on Day 14 (to allow for serial tildacerfont concentrations). Starting on Day 15, Cohorts 1 and 2 will switch to taking the study drug with their evening meal for the duration of the study.
Cohort 3 dosing:
Cohort 3 will dose with a morning meal at the study clinic on Day 1 (Visit 2) to allow for a 1-hour observational period. All subsequent doses for Cohort 3 will occur with evening meals.

APPENDIX 2. SCHEDULE OF ACTIVITIES FOR OPEN-LABEL EXTENSION FOR COHORTS 1, 1A, 2, AND 3

	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96 (EOT)	Early Termination	Safety Follow-up (Phone call)
VISIT NUMBER	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Visit windows	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**		**Last dose +30 days**
Informed consent/assent	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Pregnancy test for FOCP [1]	X	X	X	X	X	X	X	X	X	
Laboratory assessments [2, 3]	X	X	X	X	X	X	X	X	X	X[4]
PD and tildacerfont samples [5]	X	X	X	X	X	X	X	X	X	X[4]
A4-based GC dose adjustment[6]	X	X	X	X	X	X	X	X		
Weight-based tildacerfont dose adjustment	X	X	X	X	X	X	X	X		
Urinalysis [7]				X		X		X	X	X[4]
Vital signs [8], body weight	X	X	X	X	X	X	X	X	X	X[4]
Abbreviated/directed physical exam	X	X	X	X	X	X	X	X	X	X[4]
C-SSRS [9]	X	X	X	X	X	X	X	X	X	X[4]
PROMIS [10]	X	X	X	X	X	X	X	X	X	X[4]
SWYC[11]	X	X	X	X	X	X	X	X	X	

	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96 (EOT)	Early Termination	Safety Follow-up (Phone call)
VISIT NUMBER	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Visit windows	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**		**Last dose +30 days**
Bone age and predicted adult height[12]		X		X		X		X		
Dispense study drug	X	X	X	X	X	X	X	X		
Review any AEs	X	X	X	X	X	X	X	X	X	X
Study drug accountability	X	X	X	X	X	X	X	X	X	

Abbreviations: 11KT=11-ketotestosterone; A4=androstenedione; ACTH=adrenocorticotropin hormone; AEs=adverse events; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; C-SSRS=Columbia–Suicide Severity Rating Scale; ECG=electrocardiogram; EOT= end of treatment; ET=early termination; FOCP=female of childbearing potential; GC=glucocorticoid; GGT=gamma-glutamyl transferase; PD=pharmacodynamics; PROMIS= Patient Reported Outcomes Measurement Information System; 17-OHP=17-hydroxyprogesterone; SWYC=Survey of Well-being of Young Children; T=testosterone.

[1] A serum pregnancy test will be performed at Screening for FOCP only. All subsequent tests will be urine pregnancy tests

[2] Labs will be drawn at 8 AM (±1 h) before any morning dose of GC medication.

[3] Laboratory assessments include: hematology, chemistry (including liver function tests AST, ALT, ALP, GGT, total and direct bilirubin, and total bile acids), thyroid panel. Fasting is not required.

[4] As needed based upon any safety concerns, per Investigator discretion.

[5] PD Samples (ACTH, 17-OHP, A4, testosterone, and 11KT). They must be drawn prior to GC dosing. Fasting is not required. Single samples for plasma concentration of tildacerfont will be drawn at all visits.

[6] GC dose (frequency or total daily dose) may be adjusted based on A4 levels collected at each visit. If a change in GC is warranted by the A4 algorithm, sites will contact participants by telephone after receipt of results (within approximately 2 weeks) after each applicable study visit.

[7] Urinalysis should include the following: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, by dipstick. Microscopic examination should be obtained if blood or protein is abnormal.

[8] Systolic and diastolic blood pressure, pulse rate, body temperature, and respiration rate.

[9] The C-SSRS, to assess suicidality, is only conducted for participants aged 6 to 17 years.

[10] PROMIS, to assess anxiety and depression, is conducted for participants aged 5 to 17 years.

[11] The SWYC to assess anxiety and depression is only conducted in Cohort 3 participants under 5 years of age.

[12] Historical bone age and predicted adult height calculation will be performed by an x-ray of left hand and wrist to assess bone age and calculate predicted adult height.

APPENDIX 3. SCHEDULE OF ACTIVITIES FOR COHORTS 4, 5, 6, 8, 7, and 9

	Screening[1]	Treatment Period			Early Termination	Safety Follow-up[2]
		Day 1	Week 2	Week 4 (EOT)		
VISIT NUMBER	**1**	**2**	**3**	**4**		**5**
STUDY DAY	**≤14 days before V2**	**1**	**14**	**28**		**Last dose +30 days**
Visit windows			±3 days	±3 days		± 7 days
Informed consent/assent	X					
Inclusion/exclusion criteria	X	X				
Demography & medical history	X					
Review of prior medications from past year	X					
Review of concomitant medications	X	X	X	X	X	X
Hepatitis B & C and HIV Screening	X					
Pregnancy test for FOCP [3]	X	X	X	X	X	X[6]
Laboratory assessments [4, 5]	X	X	X	X	X	X[6]
Pharmacodynamics and Tildacerfont Concentration Samples (by Cohort)						
Cohorts 4, 5, 6, and 7 PD markers and tildacerfont concentration (serial, drawn together) [7] (also 8 and 9 if indicated)		X	X			
Cohorts 4, 5, 6, and 7 PD markers and tildacerfont concentration (single sample) [8] (also 8 and 9 if indicated)				X	X	X[6]
A4-based GC dose adjustment[10]				X		
Weight-based tildacerfont dose adjustment	X					
Urinalysis [11]	X		X		X	X[6]

	Screening[1]	Treatment Period			Early Termination	Safety Follow-up[2]
		Day 1	Week 2	Week 4 (EOT)		
VISIT NUMBER	**1**	**2**	**3**	**4**		**5**
STUDY DAY	**≤14 days before V2**	**1**	**14**	**28**		**Last dose +30 days**
Visit windows			±3 days	±3 days		± 7 days
Vital signs [12], body weight	X	X	X	X	X	X[6]
Physical exam [13]	X	X	X	X	X	X[6]
12-lead ECG	X		X[14]		X	X[6]
Bone age and predicted adult height[15]	X					
C-SSRS [16]	X		X	X	X	X[6]
PROMIS [17]	X		X	X	X	X[6]
SWYC[18]	X		X	X	X	X[6]
Dispense study drug[19]		X				
Study drug accountability			X	X	X	
Clinic drug administration [20]		X	X			
Review any AEs		X	X	X	X	X

Abbreviations: 11KT=11-ketotestosterone; A4=androstenedione; ACTH=adrenocorticotropin hormone; AEs=adverse events; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; CRO=contract research organization; C-SSRS= Columbia–Suicide Severity Rating Scale; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOT=end of treatment; ET=early termination; FOCP=female of childbearing potential; GC=glucocorticoid; GGT=gamma-glutamyl transferase; HIV=human immunodeficiency virus; EP=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; PROMIS=Patient Reported Outcomes Measurement Information System; 17-OHP=17-hydroxyprogesterone; SWYC=Survey of Well-being of Young Children; T=testosterone.

[1] The Screening Period may be extended as approved by the Sponsor or CRO designee.

[2] For participants continuing in the EP period, the Safety Follow-up Visit will be 30 days after their last dose in the EP Period.

[3] A pregnancy test will be performed at every visit for FOCP. The Screening Visit will include a serum pregnancy test. All subsequent visits will include urine pregnancy tests. Any positive urine pregnancy test must be followed up by a serum pregnancy test for confirmation.

[4] Labs will be drawn at approximately 8 AM (±1 h) before any morning dose of GC medication.

[5] Laboratory assessments include: A4, coagulation panel (Screening only), hematology, chemistry (including liver function tests AST, ALT, ALP, GGT, total and direct bilirubin, and total bile acids), thyroid panel. Fasting is not required.

[6] As needed based upon safety concerns, per Investigator discretion.

[7] For Cohorts 4, 5, 6, 8, 7, and 9 serial blood samples at 3 timepoints to assess PD (ACTH, 17-OHP, A4, testosterone, 11KT, cortisol) and tildacerfont concentrations following the morning (1st) dose: pre-dose (prior to GC dosing and tildacerfont dosing), 0.5 to 1.5 hours post GC and tildacerfont dose, and 3 to 5 hours post-GC and tildacerfont dose. Serial samples should be attempted in all cases but may be declined in Cohort 7 & 9 at Investigator's discretion (e.g., unable to establish IV, behavioral challenges impede collection and risk other assessments).

[8] For Cohorts 4, 5, 6, 8, 7, and 9 single blood sample to assess PD (ACTH, 17-OHP, A4, testosterone, and 11KT) and cortisol and tildacerfont concentration. Pre-dose at approximately 8 AM (±1 h), prior to GC dosing and tildacerfont dosing.

[9] Tildacerfont concentration collected prior to the morning tildacerfont and GC dose. Fasting is not required.

[10] In all cohorts, GC dose (frequency or total daily dose) may be adjusted based on A4 levels collected at Week 4 (for those participants continuing in the optional EP). If a change in GC is warranted by the A4 algorithm, sites will contact participants by telephone after receipt of results (within approximately 2 weeks) after each applicable study visit.

[11] Urinalysis should include the following: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, by dipstick. Microscopic examination should be obtained if blood or protein is abnormal. For visits in which tildacerfont is administered, urinalysis should be performed pre-dose.

[12] Systolic and diastolic blood pressure, pulse rate, body temperature, and respiration rate. Height will only be collected at Screening.

[13] Full physical exam is performed at Visit 2, EOT, and the ET Visit; an abbreviated/directed physical exam is performed at all other visits.

[14] Day 1 ECGs are conducted pre-dose. Day 14 ECG is dose independent, as participants should be at steady state.

[15] Historical bone age and predicted adult height calculation may be used if performed ≤6 months prior to Screening. If no appropriate image is available, x-ray of left hand and wrist will be performed to assess bone age and calculate predicted adult height. This may not be performed if deemed inappropriate by the investigator (based on maturation level). This will not be performed in adults (Cohorts 4 & 5).

[16] The C-SSRS, to assess suicidality, is only conducted for participants aged ≥6 years.

[17] PROMIS, to assess anxiety and depression, is conducted for participants aged ≥5 years.

[18] The SWYC to assess anxiety and depression is only conducted in Cohort 7 (and 9 if indicated) for participants ≤5 years of age.

[19] A 4-week supply of study drug will be dispensed at Visit 2 (Day 1). Participants should bring study drug to all visits for accountability. Upon receipt of study drug, the pharmacy will hold/store two doses to ensure that in-clinic dosing can occur at Visit 3 (Week 2) in the event a participant does not bring study drug to the visit.

[20] All cohorts will dose in clinic with a morning meal for their first dose to allow observation 1 hour post dose.

APPENDIX 4. SCHEDULE OF ACTIVITIES FOR EXTENSION PERIOD FOR COHORTS 4, 5, 6, 8, 7, AND 9

	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96 (EOT)	Early Termination	Safety Follow-up (Phone call)
VISIT NUMBER	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Visit windows	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**		**Last dose +30 days**
Informed consent/assent	X											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test for FOCP [1]	X	X	X	X	X	X	X	X	X	X	X	
Laboratory assessments [2, 3]	X	X	X	X	X	X	X	X	X	X	X	X[4]
PD and tildacerfont samples [5]	X	X	X	X	X	X	X	X	X	X	X	X[4]
A4-based GC dose adjustment[6]	X	X	X	X	X	X	X	X	X	X		
Urinalysis [7]				X		X	X	X	X	X	X	X[4]
Vital signs [8], body weight	X	X	X	X	X	X	X	X	X	X	X	X[4]
Abbreviated/directed physical exam	X	X	X	X	X	X	X	X	X	X	X	X[4]
C-SSRS [9]	X	X	X	X	X	X	X	X	X	X	X	X[4]
PROMIS [10]	X	X	X	X	X	X	X	X	X	X	X	X[4]
SWYC[11]	X	X	X	X	X	X	X	X	X	X	X	
Bone age and predicted adult height[12]				X		X		X		X		

	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96 (EOT)	Early Termination	Safety Follow-up (Phone call)
VISIT NUMBER	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Visit windows	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**		**Last dose +30 days**
Weight/Efficacy Tildacerfont Dose Adjustment	X		X	X	X	X	X	X	X			
Dispense study drug	X	X	X	X	X	X	X	X	X	X		
Review any AEs	X	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	

Abbreviations: 11KT=11-ketotestosterone; A4=androstenedione; ACTH=adrenocorticotropin hormone; AEs=adverse events; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; C-SSRS=Columbia–Suicide Severity Rating Scale; ECG=electrocardiogram; EOT= end of treatment; ET=early termination; FOCP=female of childbearing potential; GC=glucocorticoid; GGT=gamma-glutamyl transferase; PD=pharmacodynamics; PROMIS= Patient Reported Outcomes Measurement Information System; 17-OHP=17-hydroxyprogesterone; SWYC=Survey of Well-being of Young Children; T=testosterone.

[1] A serum pregnancy test will be performed at Screening for FOCP only. All subsequent tests will be urine pregnancy tests

[2] Labs will be drawn at 8 AM (±1 h) before any morning dose of GC medication.

[3] Laboratory assessments include: hematology, chemistry (including liver function tests AST, ALT, ALP, GGT, total and direct bilirubin, and total bile acids), thyroid panel. Fasting is not required.

[4] As needed based upon any safety concerns, per Investigator discretion.

[5] PD Samples (ACTH, 17-OHP, A4, testosterone, and 11KT). They must be drawn prior to GC dosing. Fasting is not required. Single samples for plasma concentration of tildacerfont will be drawn at all visits.

[6] GC dose (frequency or total daily dose) may be adjusted based on A4 levels collected at each visit. If a change in GC is warranted by the A4 algorithm, sites will contact participants by telephone after receipt of results (within approximately 2 weeks) after each applicable study visit.

[7] Urinalysis should include the following: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, by dipstick. Microscopic examination should be obtained if blood or protein is abnormal.

[8] Systolic and diastolic blood pressure, pulse rate, body temperature, and respiration rate.

[9] The C-SSRS, to assess suicidality, is only conducted for participants aged ≥6 years.

[10] PROMIS, to assess anxiety and depression, is conducted for participants aged ≥5 years.

[11] The SWYC to assess anxiety and depression is only conducted in Cohort 7 (and 9 if indicated) for participants ≤5 years of age.

[12] Historical bone age and predicted adult height calculation will be performed by an x-ray of left hand and wrist to assess bone age and calculate predicted adult height. This may not be performed if deemed inappropriate by the investigator (based on maturation level). This will not be performed in adults (Cohorts 4 & 5).

APPENDIX 5. PROHIBITED CONCOMITANT MEDICATIONS

Refer to Section 5.3.2 for more information on prohibited concomitant medications.

The following is a non-exhaustive list of medications that are prohibited because of their potential for metabolic interactions with tildacerfont. Most children in this study will not be taking the medications listed below. Any drugs of concern should be discussed with the MM.

alfentanil	darifenacin	itraconazole	paxlovid[a]	rivaroxaban
apixaban	diltiazem	ketoconazole	phenobarbital	sildenafil
atorvastatin	elagolix	lesinurad	phenytoin	simvastatin
avanafil	eletriptan	loperamide	posaconazole	St John's wort
avasimibe	ethinyl estradiol (>20 mcg)	lovastatin	pravastatin	teneligliptin
buspirone	felodipine	mibefradil	quetiapine	ticagrelor
carbamazepine	fluconazole	midazolam	repaglinide	triazolam
cenobamate	glyburide	nefazodone	rifampin	vardenafil
ciprofloxacin	isavuconazole	oseltamivir	rifapentine	voriconazole

[a] Study drug should be held during paxlovid treatment but can be re-started 24 hours after last paxlovid dose.

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.

APPENDIX 6. CLINICAL LABORATORY TESTS

Refer to Section 7.1.5 for more information on clinical laboratory 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	INR, PT, PTT	
Thyroid Panel	T3 (free and total), T4 (free and total), TSH	
Other Tests	Testosterone, ACTH, 17-OHP, A4, 11KT, and cortisol	
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, by dipstick Microscopic examination (if blood or protein is abnormal)	

Abbreviations: 11KT=11-ketotestosterone; A4=androstenedione; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyl transferase; INR=international normalized ratio; 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; TSH=thyroid-stimulating hormone; WBC=white blood cell.