STATISTICAL ANALYSIS PLAN

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
Study Number:	Study SPR001-205
Investigational Drug:	Tildacerfont (SPR001)
Indication:	Treatment of Classic Congenital Adrenal Hyperplasia (CAH)
Investigators:	Multicenter
IND Number:	131761
Registries	ClinicalTrials.gov: NCT05128942
Sponsor:	Spruce Biosciences, Inc. 611 Gateway Drive, Suite 740 South San Francisco, CA 94080
Plan Version:	V2.1, 24 July 2024
Original Plan Prepared by:	Inka Leprince, MS Statistical Consultant PharmaStat, LLC
Plan Update Prepared by:	Whitney S. McDonald, PhD Biometrics Consultant Spruce Biosciences, Inc.

STATISTICAL ANALYSIS PLAN

Study SPR001-205

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

Plan Version:	2.1, 24 July 2024
Plan version reviewed:	24 July 2024

Signature Page

DocuSigned by:
Whitney McDonald
26-Jul-2024

Whitney McDonald, PhD
Biostatistician
Spruce Bioscience, Inc.

Date

DocuSigned by:
Saba Sile
26-Jul-2024

Saba Sile, MD
VP, Clinical Development
Spruce Bioscience, Inc.

Date

DocuSigned by:
Will Charlton
29-Jul-2024

Will Charlton, MD
Chief Medical Officer
Spruce Bioscience, Inc.

Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Description
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
CRF1, CRF2	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
v	version
WHO DD	World Health Organization Drug dictionary

1 REVISION HISTORY

Version	Date	Document Owner	Revision Summary
1.0	08JAN2023	Inka Leprince	First version (submitted)
1.1	05MAR2024	Inka Leprince	Corrected First version (submitted)
2.0	18APR2024	Whitney McDonald	Revision

2 RELATED DOCUMENTS: PROTOCOL AND CASE REPORT FORMS

Version	Date
Protocol Version 1.0	04AUG2021
Protocol Version 2.0	27SEPT2021
Protocol Version 3.0	10MAR2022
Protocol Version 4.0	14OCT2022
Case Report Forms v7.0	21JAN2024
Protocol Version 5.0	30NOV2023

3 COMMITMENT TO GOOD STATISTICAL PRACTICE

3.1 Definition of Good Statistical Practice

The International Council for Harmonisation (ICH) Guideline on Statistical Principles for Clinical Trials (ICH E9) implicitly defines good statistical practice. Good statistical practice includes both appropriate statistical designs to minimize bias and maximize precision of analysis plus operational excellence to assure credibility of results. The scientific design associated with any clinical trial is found in the protocol. More detailed and pre-specified statistical analysis methods can be found in this statistical analysis plan.

We interpret the operational side of good statistical practice as a transparent, reproducible, and validated approach to acquiring and analyzing clinical trial data. Reproducible research depends upon process transparency and provides auditability of the statistical analysis. Analysis transparency requires that a navigable electronic process chain exists from defining the objective of the analysis to creating the results.

3.2 Use of Standards

Data standards are foundational for creating an environment where tools can be leveraged at different points in the analysis process. Data standards for clinical development of drugs have been defined and are maturing under various initiatives through the Clinical Data Interchange Standards Consortium (CDISC). Spruce Biosciences uses study data tabulation model (SDTM) data sets and Analysis Data Model (ADaM) statistical analysis files for producing analysis

results. Other applicable standards include regulatory guidance from the Food and Drug Administration (FDA) and ICH:

- ICH Guideline on the Structure and Content of Clinical Study Reports (ICH E3)
- ICH Guideline for Good Clinical Practice (ICH E6)

4 PURPOSE OF THE ANALYSIS PLAN

This statistical analysis plan (SAP) pre-specifies the statistical analysis methods for supporting the completion of a clinical study report (CSR) of Study SPR001-205 for tildacerfont, an investigational drug candidate designed to treat classic congenital adrenal hyperplasia (CAH). This SAP will be used to analyze the safety, efficacy, and pharmacodynamics (PD) data collected during the study. The planned analyses identified in this SAP may be included in regulatory submissions and/or future manuscripts.

The analysis methods described in this plan are considered *a priori*, in that they have been defined prior to clinical database lock. Exploratory analyses that are not defined in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses that are performed for the CSR, but not defined in this SAP, will be documented in the CSR. Changes from the planned analyses are described in Section 15. Should the SAP and the protocol be inconsistent with respect to any further planned analyses, the language of the SAP is governing.

The analysis of pharmacokinetic (PK) concentration data and its parameters will be documented separately. The data analysis for the open label extension period will be covered in a separate SAP.

5 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 once daily (QD), in Cohorts 1-3, for 12 weeks in children with classic CAH, and up to 400mg BID, in Cohorts 4-9, for 4 weeks in children and adults with classic CAH.

Cohorts 1 and 1a (if indicated) in children aged 11-17 years, 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. 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 subjects 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 subjects and offer recommendations on whether to proceed to Cohort 8 (11-17 years) and at what dose (300mg or 400mg BID). Following completion of the 4-week dosing period for 4 sentinel subjects in Cohort 8, the DMC will review the safety data and provide a recommendation on whether to proceed with Cohort 9 and at what dose (300mg or 400mg BID) (Table 1).

Table 1 Study Cohorts

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

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 Table 8 and Table 10. Any subject 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 subject enrolled under amendment 4 (or any other tildacerfont study) may be re-consented and enrolled under protocol amendment 5.

Clinical visits during the Treatment Period and Follow-up Period will include safety, efficacy, PK, and PD assessments. Figure 1 and Figure 2 depict study visits from Screening Period to Follow-up Period.

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

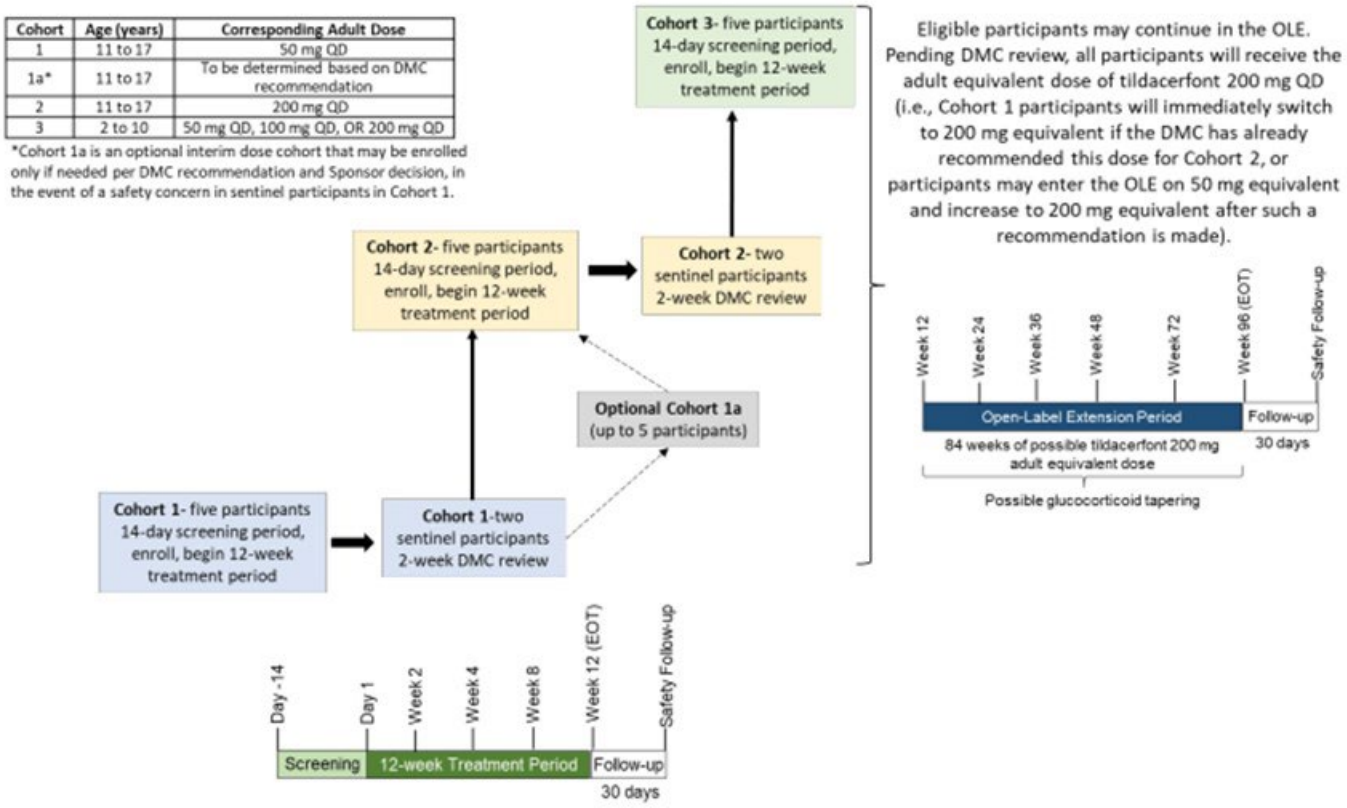
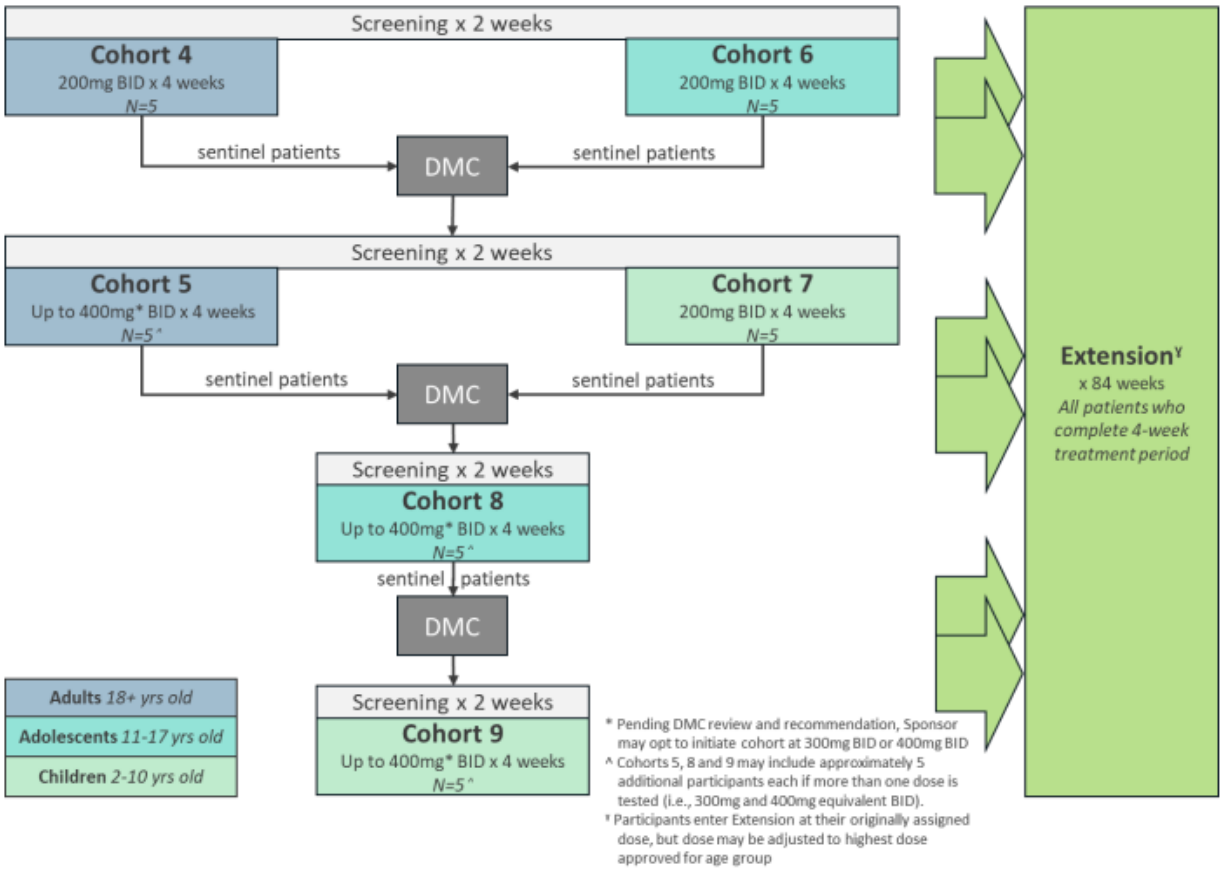


Figure 2 Overall Study Design for Cohorts 4 through 9



Assessments and procedures for evaluation of safety, efficacy, PK, and PD will be conducted per the protocol-specified schedule (see Appendix A: Schedule of Events: Table 8, , Table 10 and Table 11).

5.1 Randomization and Blinding

This study is an open-label trial with no randomization scheme.

5.2 Study Treatment

5.2.1 Study Drug Administration

Tildacerfont oral tablets will be provided in bottles of 25 mg, 50 mg and 200 mg. Subjects will take 1 to 6 tablets daily, depending on the dose and Cohort assignment. 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 meals. 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 administration of tildacerfont for Cohort 3 (Table 13).

The amount of study drug that a subject will receive will depend on the assigned dose, age, and body weight (Table 13); for subjects in Cohorts 4 to 9 the screening weight measurement will be used to determine the dose of study drug, subjects in Cohorts 1-3 dose will is adjusted as needed during each visit, and for all subjects continuing in the extension period of the study the most recent weight measurement will be used to calculate the dose of study drug.

5.2.2 Glucocorticoid Replacement Therapy

Subjects must be on a stable dose of glucocorticoid (GC) replacement therapy for at least 1 month before screening. Subjects with the salt-wasting form of CAH who take mineralocorticoids must also be on a stable dose of mineralocorticoid replacement for at least 1 month.

In all cohorts, GC dose (frequency, distribution of doses, or total daily dose) may be adjusted based on A4 levels at Weeks 4 (all subjects Cohorts 1 to 3; and subjects in Cohorts 4 to 9 if continuing in the extension) and 8 (all subjects in Cohorts 1 to 3), and Week 12 (subjects 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 Table 9 and Table 11 for schedule of events in extension cohorts).

The below A4-based algorithm will be used to guide changes to the GC replacement therapy (Table 2).

Table 2 A4-Based Glucocorticoid Dose Adjustment Algorithm

Androstenedione Levels	Change to GC Replacement Therapy
A4 ≤ upper limit of normal (ULN)	Reduce GC Dose
ULN < A4 ≤ 1.5 × ULN	Maintain GC Dose
A4 > 1.5 × ULN	Increase GC Dose

If change in GC therapy is warranted by the A4 algorithm, sites will contact subjects by telephone after the receipt of A4 results (within approximately 2 weeks) after each applicable study visit.

5.3 Assessments

Appendix A: Schedule of Events: Table 8, Table 9, Table 10 and Table 11 show the schedule of events for the study under Protocol v5.0.

5.3.1 Safety Assessments

Safety will be assessed by repeated clinical evaluations including adverse events (AEs) (serious AEs [SAEs], AEs leading to discontinuation/withdrawal, dose limiting toxicities [DLTs], AEs of special interest [AESIs]); physical examinations; vital signs; electrocardiograms (ECGs); clinical laboratory tests (chemistry, hematology, coagulation [Screening only], thyroid panel, and urinalysis); and psychiatric evaluations for suicide risk (Columbia–Suicide Severity Rating Scale [C-SSRS], Patient Reported Outcomes Measurement Information System [PROMIS] Pediatric Short Form [SF] v2.0, the PROMIS Parent-Proxy SF v2.0, or the Survey of Well-Being of Young Children [SWYC]).

The Safety Population will be used for all safety analyses. Safety data will be listed by subject 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 (Table 14), and physical examinations will be presented in listings only.

5.3.1.1 Adverse Events

Investigators will record data related to AEs, including duration, severity, relationship to study drug, action(s) taken, and outcome throughout this clinical trial. The Investigator will assess the severity of each AE according to the National Cancer Institute CTCAE version 5.0 (CTCAE 2017), summarized in Table 5 of the study protocol version 5.0. All AEs occurring in all subjects will be documented following signing of the first informed consent until approximately 30 days after the last study treatment (Follow-up Visit).

5.3.1.2 Physical Examinations

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

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

A full physical examination will be performed during the Day 1 and Week 12 visits. Abbreviated physical examinations will be performed at Screening, Week 2, Week 4, Week 8, and Safety Follow-up visits as shown in Table 8, Table 9, Table 10, and Table 11.

5.3.1.3 Vital Signs

The following vital signs will be assessed: blood pressure (systolic and diastolic; mmHg); pulse rate (beats per minute); respiration rate (breaths per minute); and body temperature (°C). Vital signs will be obtained at all clinic visits as shows in Table 8, Table 9, Table 10, and Table 11.

Total body weight (kg) will be collected at each visit. Height (cm) will be measured at Screening and every 6 months thereafter (for those enrolled in the extension). From these assessments, body mass index (BMI; kg/m^2) and body surface area (BSA; m^2) will be calculated.

5.3.1.4 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 and every 6 months thereafter (for those enrolled in the extension). Body mass index (BMI) and body surface area (BSA) will be calculated using the most recent of these measurements. In the extension period, height will need to be updated, as growth dictates changes in BSA and therefore GC dose. The most recent height and weight values will be used when BMI and BSA are reported during the extension period.

5.3.1.5 Electrocardiograms

All 12-lead ECG assessments will include: heart rate, RR, PR, QRS, QT, and QTc intervals, preferably using Fridericia's formula. ECGs will be performed at Screening, Day 1 (pre-dose), Week 2, Week 12, and Safety Follow-up visits as shown in Table 8 and Table 10.

5.3.1.6 Clinical Laboratory and Urinalysis

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 (Table 12). 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.

Clinically significant laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. All laboratory tests with values considered clinically significantly during the Treatment Period or within 30 days after the last dose of study drug should be reported as AEs and repeated at least weekly until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or MM. If such values do not return to normal/baseline within a period judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

Clinical lab assessments will be performed at all clinic visits as shown in Table 8, Table 9, Table 10, and Table 11; a complete list of clinical laboratory tests is found in Appendix 6 of study protocol version 5.0.

5.3.1.7 Psychiatric Evaluations

Subjects 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 subject's age. Any subject 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. The Columbia–Suicide Severity Rating Scale will be used during the study to monitor suicidal ideation and behavior for subjects aged 6 to 17 years old. The Baseline/Screening Version of the C-SSRS, which assesses both lifetime history and history from the last 12 months, will be used at the Screening Visit to determine subject eligibility. The Since Last Visit Version of the C-SSRS will be used at all subsequent visits (Week 2, Week 4, Week 8, and Week 12) as specified in Table 8, Table 9, Table 10, and Table 11.

5.3.1.7.1 Depression Assessment

PROMIS SF v2.0 or the PROMIS Parent-Proxy SF v2.0 will be used to monitor depression and anxiety in subjects aged 5 to 17 years old. The SWYC will be used to monitor depression and anxiety in subjects under 5 years of age. These evaluations will be conducted at Screening, Week 2, Week 4, Week 8, Week 12, and Safety Follow-up visits as shown in Table 8, Table 9, Table 10, and Table 11.

5.3.1.7.2 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 subjects 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 of the study protocol version 5.0 for depression and/or anxiety individual treatment-stopping criteria.

5.3.1.7.3 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 of the study protocol version 5.0 for depression and/or anxiety individual treatment-stopping criteria.

5.3.1.8 Dose Limiting Toxicity

A Dose Limiting Toxicity (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 subject experiences a DLT, study drug will be discontinued. DLTs are clinically significant AEs (see Protocol 5.0 Section 6.1.7). If 2 subjects in a cohort meet individual stopping criteria, the entire cohort will be stopped or dose-reduced.

5.3.2 Pharmacokinetic and Pharmacodynamic Assessments

PD hormone assessments adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17OHP), A4, and testosterone (T)will be collected Day 1, Week 2, Week 4, Week 8, and Week 12 as shown in Table 8, Table 9, Table 10, and Table 11.

6 STUDY OBJECTIVES AND ENDPOINTS

SPR001-205 is the first study of tildacerfont in children and will be used to assess safety and to determine the consistency of preliminary tildacerfont PK in pediatric subjects. The primary objective is to gain knowledge of the safety profile of tildacerfont. The secondary objectives of the study determine the consistency of tildacerfont PK in children with the current PBPK model and characterize the efficacy of tildacerfont in reducing androgen levels and reducing GC dosing based on A4 normalization over 12 weeks of treatment. Exploratory objectives include characterizing biomarker outcomes of ACTH, 17-OHP, A4, and T (Table 3).

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

6.1 Objectives and Endpoints

6.1.1 Primary

The primary objective is to evaluate the safety of tildacerfont in pediatric (ages 2 to 17 years old) and adult subjects (≥18 years old) with classic congenital adrenal hyperplasia. The primary endpoint is the occurrence of AEs and SAEs as described in Section 5.3.1.1.

6.1.2 Secondary

Secondary objectives for Cohorts 1-3 are to characterize the efficacy of tildacerfont in reducing A4 levels after 4 and 12 weeks of treatment and reducing GC dosing after 12 weeks of treatment. The associated secondary endpoints are the proportion of subjects with a reduction from baseline in A4 or a reduction in GC dosing at Week 12; and the proportion of subjects elevated baseline A4 (baseline A4 > ULN) who achieve a reduction in A4 at Week 4 or who achieve normalization of A4 at Week 4 or Week 12.

Secondary objectives for Cohorts 4-9 are to characterize the efficacy of tildacerfont in reducing A4 levels after 4 weeks of treatment. The associated secondary endpoints are the proportion of subjects with a reduction from baseline in A4 or normalization of A4 at Week 4.

6.1.3 Exploratory

Exploratory objectives include characterizing biomarker outcomes of ACTH, 17-OHP, A4, and T over the 12-week Treatment Period. The exploratory endpoints are outlined in Table 4 below.

Table 3 Objectives and Endpoints

Cohorts 1-3 (12-week Treatment)			
Objective		**Endpoint**	**Section Number**
1.	***Primary***		
1.1.	To evaluate the safety of tildacerfont in pediatric subjects with CAH	AEs and SAEs	14.1
2.	***Secondary***		
2.1.	To determine the efficacy of tildacerfont on disease control or reduction of GC use in subjects with classic CAH during 12 weeks of treatment	Proportion of subjects who achieve a reduction in A4 or reduction in GC dosing during treatment period	13.1.1
2.2.	To determine the efficacy of tildacerfont on disease control in subjects with classic CAH after 4 or 12 weeks of treatment	• Proportion of subjects with elevated baseline A4 who achieve a reduction in A4 at Week 4 • Proportion of subjects with elevated baseline A4 who achieve A4 normalization at Week 4 or Week 12	13.1.2
2.3.	To determine the consistency of preliminary tildacerfont PK in subjects with those simulated in a PBPK model	Tildacerfont plasma concentrations will be compared with the current PBPK simulation for consistency	Provided in a separate SAP
3.	***Exploratory***		
3.1.	To explore changes in PD biomarkers in pediatric subjects with CAH	Change from baseline in adrenocorticotropic hormone (ACTH), 17hydroxyprogesterone (17-OHP), A4, and testosterone	13.2.1
COHORTS 4, 5, 6, 8, 7, and 9 (4-week Treatment)			
4.	***Primary***		
4.1	To evaluate the safety of tildacerfont in subjects with CAH	Adverse events (AEs) and serious adverse events (SAEs)	14.1
5.	***Secondary***		
5.1	To determine the efficacy of tildacerfont on disease control in subjects with classic CAH after 4 weeks of treatment	• Proportion of subjects who achieve reduction in androstenedione (A4) at Week 4 • Proportion of patients who achieve A4 normalization at Week 4.	13.1.1
5.2	To determine the consistency of preliminary tildacerfont pharmacokinetics (PK) in subjects with those simulated in a physiologically based PK (PBPK) model	Tildacerfont plasma concentrations will be compared with the current PBPK simulation for consistency	Provided in a separate SAP
6.	*Exploratory*		
6.1	To explore changes in pharmacodynamic (PD) biomarkers in subjects with CAH	Change from baseline in adrenocorticotropic hormone (ACTH), 17hydroxyprogesterone (17-OHP), A4, testosterone	13.2.1

EXTENSION (Cohorts 1-9)			
7.	***Primary***		
7.1	To evaluate the safety of tildacerfont in subjects with CAH	AEs and SAEs	14.1
8.	***Secondary***		
8.1	To determine the efficacy of tildacerfont on reduction of glucocorticoid (GC) use in subjects with classic CAH after 4 weeks or 12 weeks of treatment	• Proportion of subjects who achieve reduction in glucocorticoid (GC) dosing (beyond 12 weeks for Cohorts 1-3 and beyond 4 weeks for Cohorts 4-9) • Proportion of subjects who achieve approximately physiologic GC dosing ($\leq$ 11 g/m^2/d)	13.1.1
8.2	To determine the efficacy of tildacerfont on disease control in subjects with classic CAH	• Proportion of subjects 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 subjects with elevated A4 at completion of treatment period who achieve A4 normalization	13.1.2
9.	**Exploratory**		
9.1	To explore changes in pharmacodynamic (PD) biomarkers in pediatric subjects with CAH	Change from baseline in adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17-OHP), A4, testosterone, (at Week 4 for all cohorts and Week 12 for Cohorts 1-3)	13.2.1
9.2	To explore the impact of tildacerfont on skeletal maturation	Change from baseline in predicted adult height	5.3.1.4

Table 4 Detailed Exploratory Objectives and Endpoints

Objective		Endpoint	Section Number
1.	***Change from baseline over 12 weeks***		
1.1.	To explore changes from baseline in pharmacodynamic (PD) biomarkers in pediatric subjects with CAH over 12 weeks	Log-transformed change from baseline in ACTH	13.2.1
1.2.		Log-transformed change from baseline in 17-OHP	13.2.1
1.3.		Log-transformed change from baseline in A4	13.2.1
1.4.		Log-transformed change from baseline in T, by sex	13.2.1
2.	***Change from baseline in ratios over 12 weeks***		
2.1.	To explore changes in select PD biomarkers ratios in pediatric subjects with CAH over 12 weeks	Change from baseline in A4/T ratio (males only)	13.2.2
3.	***Proportion of subjects with reduction*** ***[1] overall and*** ***[2] by subgroup (Baseline A4 ≤ ULN; Baseline A4 > ULN)*** ***[3] by subgroup (Male; Female)***		
3.1.	To explore the proportion of subjects with changes in PD biomarkers at Week 4, Week 8, and Week 12	ACTH [a] any reduction; [b] ≥ 50% reduction; [c] ≤ ULN	13.2.3
3.2.		17-OHP [a] any reduction; [b] ≥ 50% reduction; [c] ≤ ULN	13.2.3
3.3.		A4 [a] any reduction; [b] ≥ 50% reduction; [c] ≤ ULN	13.2.3
3.4.		Testosterone by sex [a] any reduction; [b] ≥ 50% reduction; [c] ≤ ULN	13.2.3
4.	***Change from baseline in GC total daily dose at Week 12***		
4.1.	To explore changes in GC total daily dose at Week 12	Change from baseline (mg)	13.2.4
4.2.		Change from baseline adjusted for body surface area (mg/m^2)	13.2.4
4.3.		Percent change from baseline	13.2.4
4.4.		Proportion of subjects with GC reduction	13.2.4
4.5.		Proportion of subjects who decrease frequency of administration	13.2.4

7 SAMPLE SIZE AND POWER

No formal sample size calculation was performed. A sample size of up to approximately 55 children (i.e., 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 population and provide data to support the continued use of the PBPK model to determine pediatric dosing requirements in future studies. Although this is a pediatric study, up to 15 adults are included in this study to allow for all new dosing regimens to be tested in adults prior to children. The safety profile of tildacerfont in adults will primarily be established in other studies.

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 subjects), 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. Up to a total 70 subjects will be enrolled in the study. Please see Table 1 for subject numbers by dosing cohort:

8 ANALYSIS SETS

The Safety (SAF) Analysis Set is defined as all subjects who receive at least one dose of study drug. This will be the primary analysis set for general and safety analyses.

The Pharmacokinetic (PK) Analysis Set will include all subjects in the Safety Analysis Set with at least one post-dose PK sample above the limit of quantification.

The Pharmacodynamic (PD) Analysis Set will include all subjects in the Safety Analysis Set with a baseline A4 assessment or GC dose and at least one evaluable post-baseline A4 assessment.

The Elevated Baseline Pharmacodynamic (EBPD) Analysis Set will include all subjects in the PD analysis set whose baseline A4 assessment is greater than the upper limit of normal.

9 GENERAL CONSIDERATIONS

Data summarization and presentation conventions are documented in a separate document for mock-shells.

9.1 Presentation of Summary Statistics

For most summary statistics, data will be analyzed and displayed in tabular format.

Unless otherwise specified, continuous PD hormones (Section 5.3.2) will be summarized using a 11-point descriptive statistics (i.e., n, mean, standard deviation [SD], median, 25% quartile [Q1],

75% quartile [Q3], minimum, maximum, geometric mean, geometric coefficient of variance [CV%], 95% confidence interval [CI] for geometric mean [including geometric mean ratio and its 95% CI]).

All other continuous variables will be summarized using an 8-point descriptive summary (n, mean, SD, median, Q1, Q3, minimum, and maximum) unless otherwise specified.

The same number of decimal places observed in the source data will be presented when reporting minimum and maximum; 1 additional decimal place than in the source data will be presented when reporting mean, median, Q1, Q3, geometric mean, 95% CI; 2 additional decimal places than in the source data will be presented when reporting SD. Geometric CV% will be reported to one decimal place.

All categorical/qualitative data will be presented using the frequency of events and percentages. All percentages will be presented to 1 decimal place, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies. For summaries of AEs and CMs, the percentages will be based on the number of subjects who received study drug. All analyses and summaries will be produced using SAS® version 9.4 or higher (SAS Institute Inc, Cary, North Carolina, USA).

9.2 Re-Enrolled Subjects

9.2.1 Re-Enrolled, Same Cohort

As of the writing of this SAP, there are two subjects, 00003-1001 and 00003-1002, who reenrolled into Cohort 1 under Protocol Amendment 3 which was originally designed as a PK study. Two months after completing the 14-day Treatment Period, these two subjects re-enrolled into Cohort 1 under Protocol Amendment 4. Due to the different protocol specified visits (i.e., a 14-day Treatment Period extended to a 12-week Treatment Period substituted with a single pre-dose assessment), time points (i.e., the 8AM, 10AM, 14-hours post dose, and 16-hours post dose time points substituted by a single pre-dose assessment), laboratories (i.e., Mayo Clinic changed to Associated Regional and University Pathologists Pharmaceutical Product Development), and methods (i.e., liquid chromatography with tandem mass spectrometry changed to high performance liquid chromatography with tandem mass spectrometry), the subjects' initial Cohort 1 Protocol Amendment 3 experiences will not be included in efficacy analyses, but will be included in listings. For safety analyses, each enrollment experience will be summarized (subjects will be counted twice).

9.2.2 Re-Enrolled, Different Cohort

Re-enrolled subjects will have more than one set of cohort data. Therefore, the summary results by cohort will be summarizing these subjects by unique enrollment experience (per cohort) rather than per subject for summaries of disposition, protocol deviations and study drug exposure. Subjects who re-enrolled into two or more different cohorts will have multiple baseline values for safety and efficacy summaries – a set of baseline values for their first cohort experience, and a set of baseline values for each subsequent cohort experience.

9.3 Reporting

Results of statistical analyses will be reported using summary tables, listings, and figures (TLFs). The ICH of Technical Requirements for Pharmaceuticals for Human Use numbering convention will be used for all CSR TLFs.

9.4 Definitions and Derived Variables

9.4.1 Screened Subjects

Subjects who signed an informed consent form are considered Screened Subjects

9.4.2 Enrolled Subjects

Subjects who receive study drug treatment are considered enrolled subjects.

9.4.3 Study Day

Study Day, which follows the CDISC SDTM standard, is defined as (Assessment date of first study drug dosing + 1 day), where the assessment date is on or after the date of first study drug dosing; (Assessment date - date of first study drug dosing), where the assessment date is before the date of first study drug dosing.

9.4.4 End of Study Treatment Definition

A subject in Cohorts 1-3 will have completed the main study treatment period if they completed the Visit 6 (Week 12) Visit. A subject in Cohorts 4-9 will have completed the main study treatment period if they completed the Visit 4 (Week 4) Visit.

9.4.5 End of Study Definition

A subject will have completed the study if the subject has completed the Follow-up Visit.

9.4.6 Body Mass Index

Body mass index (kg/m^2) is derived as weight (kg) / [height (m) × height (m)]. The most recent height measured will be used in all BMI calculations.

9.4.7 Body Surface Area

Body surface area is calculated per the Mosteller formula as sqrt((height (cm) × weight(kg))/3600), rounded to one decimal place. The most recent height measured will be used in all BSA calculations.

9.4.8 Tanner Stages

The Tanner scale is a 5-point scale that is used to describe the onset and progression of pubertal changes in children, with a value of 1 indicating pre-adolescent and a value of 5 indicating mature, adult development. Tanner stages 1-5 are collected for all pediatric patients at 6-month

intervals. Once a Tanner stage of 5 is recorded, no further Tanner staging will be required, and all subsequent values will be recorded as stage 5.

9.4.9 Baseline Values

Baseline values are defined as the last non-missing assessment that is on or prior to the date of the first dose of study drug in each cohort. If the date and time of an assessment are collected, then the date and time are compared against the first dose date and time; otherwise, if only the date of an assessment is collected, the baseline assessment will be the last non-missing assessment collected on or prior to the date of the first dose of study drug. A4, 17-OHP, and ACTH baseline values are defined as the mean of measurements collected between Screening (Visit 1) and Day 1 (Visit 2).

Subjects who re-enrolled into the same cohort, the last-non-missing assessment prior to the second enrollment's first dose of study drug will be used as baseline.

9.4.10 Change from Baseline

$$Baseline\ Change_i = Value_i - Baseline$$

Change from baseline is post-baseline assessment subtracted by the baseline assessment.

9.4.11 Percent Change from Baseline

$$Baseline\ Change\ (\%)_i = (Baseline\ Change_i / Baseline)$$

Percent change from baseline is calculated as the change from baseline divided by the baseline assessment and multiplied by 100%.

9.4.12 Change from Baseline on the Log Scale

$$\log Baseline\ Change_i = \log Value_i - \log Baseline$$

$$= \log\left(\frac{Value_i}{Baseline}\right)$$

The change from baseline on the log scale is calculated as log(post-baseline assessment) subtracted by the log(baseline assessment). It is also mathematically equivalent to the log of the ratio of the post-baseline assessment divided by the baseline assessment.

9.4.13 Geometric Mean Ratio and Percent Change

For PD hormone variables (Section 5.3.2), the geometric mean ratio (GMR) and percent change from baseline will be calculated by cohort and dose level. The GMR is derived from the natural logarithm of the post-baseline value divided by the baseline value [log(post-baseline/baseline)]. The GMR is the exponential function of the mean of log(post baseline/baseline). The 95% CI of GMR is the exponential function of the 95% CI of the mean [log(post baseline/baseline)]. The percent change is derived as 100 × (GMR - 1). The 95% CI of percent change is 100 × (95% CI of GMR - 1).

9.4.14 Responder Definitions

The second secondary efficacy and exploratory variables are proportions of responders based on serum PD assessments and GC dosing. Indicator variables for each responder criteria are defined in Table 5.

Table 5 Responder Definition by Endpoint

Endpoint	Definition	
Composite: Proportion of subjects who achieve reduction in A4 *OR* reduction in GC dosing (Cohorts 1 through 3) at a postbaseline visit	1	Reduction in A4 OR reduction in GC Dose
	0	(no reduction in A4 AND no reduction in GC Dose) OR missing
Proportion of subjects with elevated baseline A4 who achieve a reduction in A4 at a post-baseline visit	1	Baseline*A*4 > ULN AND reduction in A4
	0	Baseline *A*4 ≤ ULN OR no reduction in *A*4 OR missing
Any reduction at a postbaseline visit	1	Reduction from baseline
	0	No reduction from baseline OR missing
≥ 50% reduction at a postbaseline visit	1	≥ 50% reduction from baseline
	0	< 50% reduction from baseline OR missing
≤ ULN at a post-baseline visit	1	≤ ULN
	0	> ULN OR missing

9.4.15 Study Drug Exposure Variables

9.4.15.1 Nominal Tildacerfont Dose (mg)

The nominal tildacerfont dose is collected in “Pediatric weight-based dosing (mg)” question in the Drug Accountability Cohort 1 eCRF form and the Drug Accountability eCRF form, respectively.

9.4.15.2 Tildacerfont Dose Adjusted for Body Weight (mg/kg)

For a given dispensation visit, the concurrently measured weight as measured in the Vital Signs CRF form will be used to calculate the tildacerfont dose adjusted for body weight by dividing the nominal tildacerfont dose (mg) by weight (kg) (Table 13).

9.4.16 Prior, Concomitant and Post treatment Medications

Prior medication is any medication that is taken within a year prior to the first study drug dosing.

A concomitant medication (CM) is any medication the subject is taking, other than tildacerfont during the study. CMs are medications: that are continued from Screening and continued after the first study drug dosing, or with start dates or stop dates within the first dose date through last dose date + 24 hours, missing CM end date, or ongoing within the study.

Post medications are any medication taken after the last study drug dose date + 24 hours, missing CM end date, or ongoing.

9.4.16.1 Prohibited Concomitant Medications

Prohibited and cautionary concomitant medications are those medications with their potential for metabolic interactions with tildacerfont. Specific definitions are in Table 14, which provides a non-exhaustive list of medications.

9.4.17 Glucocorticoid Therapy

GC therapies are concomitant medications that fall under the Anatomical Therapeutical Chemical (ATC) classification is “Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins” or “Glucocorticoids” as collected in the Concomitant Medication eCRF form.

9.4.17.1 Glucocorticoid Dose in Hydrocortisone Equivalents

Table 6 defines the potencies of various GCs relative to HC in treating CAH. These conversion factors will be used to standardize and determine whether a subject’s daily GC dose satisfies study eligibility criteria and provide general guidelines for GC tapering.

Table 6 Relative Potencies of Glucocorticoids in Hydrocortisone Equivalents

Glucocorticoid	Potency in CAH (HCe)
HYDROCORTISONE	1
PREDNISONE	4
PREDNISOLONE	5
PREDNISOLONE SODIUM PHOSPHATE	5
METHYLPREDNISOLONE	5
TRIAMCINOLONE	5
DEXAMETHASONE	70
CORTEF	1
HYDROCORTISONE (ALKINDI SPRINKLES)	1
CORTISONE ACETATE	0.8

9.4.17.2 Glucocorticoid Body Surface Area Based Dose

The baseline GC BSA-based dose is calculated as the GC dose (Section 9.4.17.1) divided by the body surface area (Section 9.4.7) at the corresponding time point, rounded to two decimal places.

9.4.17.3 Glucocorticoid Dose at Visit

Based on the GC therapies collected in the A4-based GC Dose Adjustment eCRF form, GC dose at visit is collected under the question, "Total GC Dose (mg)".

9.4.17.4 Baseline Glucocorticoid Dose

The GC dose at Day 1 (baseline) is assumed to be the same dose at Week 4.

9.4.18 Adverse Events

AEs are any untoward medical occurrence in a subject participating in a clinical trial with onset date from the signing of the informed consent/assent until the end of the follow up period.

TEAEs are defined as any AEs, regardless of relationship to study drug, which have an onset or worsening in severity on or after the first dose of study drug until 30 days after the final dose of study drug (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) will be specified and used for comparison. If a subject discontinues study drug but remains in the study, AEs with onset date after 30 days of last dose of study drug until the end of the follow up period will be considered post-treatment adverse events.

Related TEAEs are those reported by investigators as possibly related, probably related, or definitely related to the study drug.

AESIs are events that do not meet SAE criteria but must be monitored on an ongoing basis as defined in the Study Protocol Section 7.2.8 and identified in the AE eCRF page.

Serious AEs (SAEs) are defined in the Study Protocol Section 7.2.6 and identified in the AE eCRF page.

Dose-limiting toxicities (DLTs) are defined as a Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher TEAE that is also considered at least possibly related to study drug.

Suspected unexpected serious adverse reactions is an AE that is serious, related to study drug, and is not expected in the targeted disease (classic CAH).

9.5 Analysis Windows

Protocol-specified visits and unscheduled clinical visits may be used to capture missed or partially completed clinical visits; therefore, analysis visits and their windows are defined using Study Day (See Section 9.4.3). For the purposes of data analysis and summary, assessments and

measurements will be preferentially flagged based on the collection date/time that is closest to the protocol-scheduled time point (or target Study Day). Analysis visit windows are presented in Table 7.

Table 7 Analysis Visit Windows

Protocol Specified Visit Number	Analysis Visit	Target Study Day	Start (days)	Stop (days)
1	Screening	-15	low	-1
2	Day 1	1	1	8
	Day 2	2		
	Day 8	8		
	Day 14	14		
3	Week 2	15	9	22
4	Week 4	29	23	43
5	Week 8	57	44	71
6	Week 12	85	72	127
7	Week 24	169	128	211
8	Week 36	253	212	295
9	Week 48	337	296	421
10	Week 60	421	341	501
11	Week 72	505	411	599
12	Week 84	589	481	697
13	Week 96	673	551	Last Dose Date + 3 days
7	Follow-up	Last Dose Date + 30		

10 GENERAL CONSIDERATIONS

10.1 Adjustments for Covariates

Due to the limited size of the sample and the exploratory nature of this trial, adjustments for covariates may introduce potential biases or limitations. Therefore, summaries of secondary and exploratory efficacy endpoints may be generated without incorporating covariates such as age group, gender, and pubertal status. The trends in these covariates may be evaluated in summaries by subgroup as specified in supportive sections of the efficacy endpoints (Sections 13.1.1.3 and 13.2).

10.2 Handling Dropouts or Missing Data

Every effort will be made by the Sponsor to ensure completeness of data collection. Missing data will not be imputed unless otherwise specified.

10.2.1 Handling of Laboratory Data

For non-PK laboratory values that are continuous in nature and either above or below the respective quantitation limits (X), the following imputations will be made for the purposes of summarization:

- If a value is reported as '< X', then the imputed value will be X/2
- If a value is listed as =X, then the imputed value will be X
- If value is reported as '> X', then the imputed value will be X+1

10.2.2 Handling of Safety Data

10.2.2.1 Adverse Events

In the event that the time of AE onset (before or after intake of study drug) cannot be determined and if an AE is treatment-emergent because of a partial onset date, the event will be counted as a TEAE. Adverse events with incomplete onset and end dates will have their dates imputed and then treatment-emergent status will be evaluated.

Incomplete adverse event onset date/time:

- If day is missing:
  - If month and year are the same as the month and year of first study drug exposure, then impute to the date of first study drug exposure.
  - Else if day is missing and year or month is not the same as the year and month of first study drug exposure, then impute as Day 1 of the month.
- If month is missing:
  - If year is the same as the year of first study drug exposure, then impute to the date of first study drug exposure.
  - Else if year is different from the year of first study drug exposure, then impute as January 1.

- If year is missing, then impute to the date of first study drug exposure.
- If imputed start date is after AE end date, then impute the start date to the AE end date.

Incomplete adverse event end date/time:

- If only have a YEAR, impute as December 31.
- Else if only have YEAR and MONTH, then impute to last day of the month.
- Otherwise missing, no imputation.

If severity or relationship of an AE to study drug is not recorded, the severity or relationship will be imputed as "severe" or relationship as "possibly related," for analysis purposes. All efforts will be made to ensure no missing severity or relationship of an AE to study drug prior to database lock finalization.

10.2.2.2 Concomitant Medications

If the start date of a medication is missing, the medication will be considered to have started prior to the study. Such a medication may also be considered concomitant, depending on the stop date or lack thereof. If the stop date of a concomitant medication is missing, then the medication will be treated as ongoing. If the start date of a medication is missing, the stop date will be used to determine whether it is concomitant. Medications with other incomplete start dates or end dates will be imputed as follows:

Incomplete medication start date/time:

- If only have a YEAR, impute as January 1.
- Else if only have YEAR and MONTH, impute as Day 1 of month.
- Otherwise missing, no imputation. Incomplete medication end date/time:
- If only have a YEAR, impute as December 31.
- Else if only have YEAR and MONTH, then impute to last day of the month.
- Otherwise missing, no imputation.

10.3 Primary Analyses

The primary analyses will be conducted when all subjects complete Week 12 of study treatment and the study and the data has been frozen for analysis.

10.4 Multicenter Considerations

This is a multicenter trial in the United States. Data from all study centers will be pooled for efficacy and safety analyses. Because the number of subjects at each center is likely to be small, no analyses will be performed by the center.

10.5 Multiple Comparisons, Multiplicity

This Phase II study is exploratory in nature and no adjustment for multiplicity is planned. The existence of multiplicity is acknowledged, and interpretation of the secondary and exploratory results will be interpreted with caution.

10.6 Active-Control Studies

Since all subjects will receive open-label study drug, there is no placebo group to serve as a comparator in this study.

10.7 Examination of Subgroups

Subjects will be categorized into the following common subgroups for the purposes of evaluating the pharmacodynamic endpoints. Due to the small sample size, subgroups will be summarized descriptively in place of subgroup analyses.

- Baseline A4 (≤ ULN; > ULN)
- Sex (Male, Female)

11 STUDY SUBJECTS

11.1 Subject Enrollment and Disposition

Screening and disposition will be summarized study-wide and by cohort.

Enrollment and disposition will be summarized by cohort and overall. Dose discontinuations and reasons for study drug discontinuation will be listed and summary tables.

A subject listing with enrollment, disposition, dose, dose discontinuations, site ID, date of informed consent, and reason for screen failure for subjects who were screened but not enrolled will be generated.

A separate listing will display subjects who are excluded from SAF and PD analysis sets, along with reasons for the exclusions.

11.2 Protocol Deviations

Any CSR-reportable protocol deviation will be documented, and its impact on population for any patient will be specified. Numbers and percentages of patients with CSR-reportable protocol deviations will be summarized by deviation type (e.g. major) and category (e.g. noncompliance with study procedures or restrictions). All deviations will be identified prior to database lock and will be summarized and presented in listing(s); listings will include flags for deviation type (major or minor). Major protocol deviations are defined per Guideline for Industry: Structure and Content of Clinical Study from (ICH E3) guidance.

11.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and listed for the Safety Population.

11.3.1 Demographics

Demographic characteristics will include age, age category (2 – 5 years, 6 – 10 years, 11 – 17 years, and ≥ 18 years), sex, child-bearing potential, race, and ethnicity. Demographic characteristics will be summarized by cohort and overall. A subject listing of demographics will be provided.

11.3.2 Baseline Characteristics

The following baseline characteristics include baseline weight, height, BMI, BSA, and PD hormones (A4, A4 category [< ULN; ≥ ULN], ACTH, 17-OHP, and testosterone), and GC regimen. Baseline characteristics will be summarized by cohort and baseline characteristics listing by subject will be provided.

11.4 Medical History

General medical history will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA®) Dictionary (version 24.1). General medical history will be summarized by cohort, system organ class (SOC), and preferred term (PT) for the Safety Population. A subject listing of general medical history will include cohort, start date/end date, verbatim medical history term, SOC, PT, and ongoing status.

12 STUDY DRUG AND OTHER MEDICATIONS

12.1 Exposure to Study Drug

The drug accountability information, including number of tablets dispensed, number of tablets returned, and number of tablets lost or destroyed, nominal tildacerfont dose (Section 9.4.15.1), and dose adjusted for body weight (Section 9.4.15.2) will be presented in subject listings.

12.2 Prior and Concomitant Medications

All medication verbatim terms reported on the eCRFs will be mapped according to the World Health Organization (WHO) Drug Dictionary (WHO D Global-B3 Sep2021). The medications will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and preferred names.

All medications will be provided in a subject listing with variables including, but not limited to: Start date/end date/ongoing, medication name, ATC class and preferred name, indication, dose, unit, form, frequency, and route.

12.3 Glucocorticoid Regimen

Concomitant GC therapy will be summarized for each cohort of the study. The source of GC dosing is the A4-based GC Dose Adjustment eCRF.

Descriptive statistics for GC dose (in mg HCe) and BSA-adjusted GC dose will be summarized by cohort and scheduled time point. In addition, the number and percentage of subjects who

decrease their dose of GC regimen will be summarized by cohort. All the above information will be included in a subject listing.

13 EFFICACY ANALYSES

The efficacy analyses will exclude data collected under Protocol v3.0.

The efficacy analyses are planned after all subjects have completed the study treatment and the database is frozen. The scheduled visits included in this treatment period can be found in Table 7.

13.1 Secondary Efficacy Analysis

The secondary "treatment policy" estimands are evaluated by two secondary efficacy assessments.

13.1.1 Reduction in A4 or Reduction in GC Dosing at Week 12

Population: The analysis population for the secondary efficacy analyses is the PD analysis set.

Variable: The analysis variable is the proportion of subjects in the PD analysis set who are responders (defined in Table 5). This proportion is calculated for each cohort as the number of subjects at Week 12 (at Week 4 for cohorts 4 through 9) who have a reduction of A4 or reduction in GC reduction, divided by the total number of subjects in the PD analysis who were enrolled in each cohort. This proportion is also calculated to evaluate the overall subjects at Week 12 (at Week 4 for cohorts 4 through 9) by pooling the responders and dividing by the total number of subjects in the PD analysis set.

Subjects with missing A4 or GC dosing information at a given visit are assumed to be non-responders at that visit. Subjects who do not have a reduction from baseline in A4 or a reduction in GC dose are considered non-responders.

13.1.1.1 Reporting Results

13.1.1.1.1 Descriptive Statistics

Frequency and proportion (expressed as percentages) of responders will be calculated along with 95% Exact (Clopper-Pearson) CIs and reported for the study and each cohort.

13.1.1.1.2 Graph Presentation

The proportion of responders will be displayed graphically over time with the y-axis representing the proportion meeting the responder definition and the x-axis the visits Week 8 and Week 12.

Bar charts with one bar per cohort will display the proportions of responders at a Week 12. This bar chart may be replicated at the additional time point listed below.

13.1.1.3 Supportive Summaries

13.1.1.3.1 Subgroups

The proportion of responders of the planned subgroup analyses (Section 10.7) will be summarized.

13.1.1.3.2 Additional Timepoints

The proportions of responders at the post-baseline protocol scheduled visits will be summarized (Week 8).

13.1.2 Elevated Baseline A4 who Achieve a Reduction in A4 at Week 4

Population: The analysis population for the secondary efficacy analyses is the EBPD analysis set.

Variable: The analysis variable is the proportion of subjects in the EBPD analysis set who are responders (defined in Table 5). This proportion is calculated for each cohort as the number of subjects at Week 4 who have a reduction of A4, divided by the total number of subjects in the EBPD analysis who were enrolled in each cohort.

Subjects with missing data at a given visit are assumed to be non-responders at that specific visit. Subjects who do not have a reduction from baseline in A4 are considered non-responders.

13.2 Exploratory Efficacy Analysis

13.2.1 Change from Baseline in PD Biomarkers

The PD analysis set will be used for exploratory efficacy analyses.

Descriptive statistics (11-point) for the exploratory biomarker assessments, change from baseline, percent change from baseline, and geometric mean ratio will be presented by cohort, scheduled time points including Baseline, and by subgroup (Section 10.7). PD biomarkers include ACTH, 17-OHP, A4, and testosterone.

The back-transformed log scale change from baseline and 95% confidence intervals will be calculated for each post-baseline visit by cohort and overall using a balanced bootstrap method. The bootstrapping will consist of 1,000 replicate samples using a uniform random number generation by the method of Fishman and Moore with a SEED = 42, where the sampling unit is the subject ID which uniquely identifies each enrollment experience for a given subject.

13.2.2 Change from Baseline in PD Biomarker Ratios

The change from baseline in select PD ratios will also be summarized and listed:

- A4/T (males only)

13.2.3 Proportion of Subjects with Reduction in PD Biomarkers

The frequency and proportion (expressed as percentages) and the Exact 95% CI of subjects with a reduction (any reduction; ≥ 50% reduction; normalization [≤ ULN]) in PD biomarkers at Weeks 4 through Week 12 will be summarized descriptively overall, by cohort, and by subgroup (Section 10.7).

13.2.4 Change from Baseline in Glucocorticoid Total Daily Dose

The following metrics of GC reduction include change from baseline (mg in HCe), change adjusted for BSA (mg/m^2), and percent change from baseline. These measurements of change from baseline in GC total daily dose at Week 12 will be summarized by cohort and overall. A listing of GC reduction will be provided.

The proportion of subjects who achieve the following criteria will be summarized in a table with descriptive statistics by cohort and scheduled time point:

- Any GC reduction
- ≥ 1 mg/m^2 GC reduction or any reduction from baseline in A4 at Week 12 (secondary efficacy endpoint).

A listing of prior and concomitant GC medications will provide information about subjects whose baseline dosing > 3 × daily decreases frequency of administration ≤ 3 x daily.

14 SAFETY ANALYSIS

The Safety Population will be assessed for AEs, SAEs, AEs leading to discontinuation/withdrawal, DLTs, AESIs, physical examination, vital signs, ECGs, and clinical laboratory tests. All analyses of the safety data will be performed by adult equivalent dose levels. Urinalysis, psychiatric evaluations, and concomitant medications will be presented in listings only.

14.1 Adverse Events

All AE verbatim terms reported on the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA® version 24.1).

All reported AEs (including non-TEAEs) will be listed. Separate listings will be provided for SAEs, TEAEs leading to study drug discontinuation, DLTs, AESIs, and AEs related to COVID-19.

All TEAE counts will be by enrollment experience (re-enrollers will be counted once per enrollment) and not by event. Subjects reporting the same TEAE on multiple occasions will have, the highest severity (severe > moderate > mild) or study drug relationship (related > probable > possible > unlikely > unrelated) recorded for the event in each enrollment experience will be summarized. All AE summary tables will display the number and percentages of subjects per enrollment experience reporting TEAEs, unless otherwise specified.

An overall summary of AEs will be reported and will include the number and percentage of subjects experiencing any AEs, SAEs, TEAEs, TEAEs by maximum severity (highest toxicity grade), study drug related TEAEs by maximum severity (highest toxicity grade), study drug related SAEs, DLTs, AESIs, TEAEs leading to study drug discontinuation, and TEAEs leading to deaths.

The number and percentage of subjects experiencing each TEAE, study drug related TEAE, and SAEs will be displayed in summary tables by adult equivalent dose levels as well as by cohort according to system organ class and preferred term. Tables including only preferred term summarized by adult equivalent dose levels as well as by cohort for the number and percentage of subjects experiencing each TEAE will be presented.

14.2 Clinical Laboratory Evaluation

Laboratory parameters chemistry, hematology, coagulation, and thyroid panel will be displayed in summary tables by cohort and scheduled time point and will include both observed values and change from baseline values. As applicable, a summary of laboratory parameters will also be displayed in a shift table of baseline values relative to normal ranges (low, normal, high, missing). Subject-level listings for urinalysis and all laboratory parameters (see Table 12) will be provided. A separate listing will include abnormal clinical laboratory test results. In addition, subjects concurrently meeting the following Hy's law criteria at any assessment date will be identified and listed:

- Alanine aminotransferase (ALT) > 3 × ULN
- Aspartate aminotransferase (AST) > 3 × ULN
- Total bilirubin (TBL) > 2 × ULN

14.3 Vital Signs

Pulse rate, respiratory rate, temperature, including baseline values and change from baseline values, will be summarized with descriptive statistics by cohort and scheduled time point. All vital signs parameters will be listed.

14.4 12-Lead Electrocardiogram

Electrocardiogram (ECG) data, such as clinical interpretation of ECGs, heart rate (HR) values, and interval assessments of RR, PR, QRS duration, QT interval, and the Fridericia's corrected value of the interval between the Q and T waves on the ECG tracing will be listed. Descriptive statistics for observed values and change from baseline will be summarized by cohort and scheduled time point for these 12-lead ECG interval and HR assessments.

The number and percentage of subjects meeting potentially clinically significant QTcF assessments (> 60 increase from baseline; > 450 msec in males; >460 msec in females) will be summarized by cohort.

14.5 Psychiatric Evaluations

The psychiatric evaluation assessments of suicidality, depression, and anxiety will be listed.

15 CHANGES RELATIVE TO THE PROTOCOL-SPECIFIED ANALYSIS

Study Protocol Section 8.2 defines the PD population as including "all subjects in the Safety Population with at least 1 evaluable post-baseline PD assessment." Given the vague language in the protocol of how to determine eligibility for the PD population – if for example a subject must have a non-missing post-baseline from all six hormones (ACTH, 17-OHP, A4, testosterone, and 11KT), of any of the six PD hormones, or one specific hormone, the SAP added the specificity that the PD population includes "all subjects in the Safety Analysis Set with a baseline A4 assessment and at least one evaluable post-baseline PD A4 assessment" to align with the A4-dependent secondary efficacy analyses.

SAP Section 8 additionally defines the Elevated Baseline Pharmacodynamic Analysis Set to support the secondary efficacy analysis of subjects with elevated baseline A4 who achieve a reduction in A4 at Week 4.

The Study Protocol Section 8.3.6 specifies that the hormone,11-ketotestosterone (11-KT), will be summarized as part of the pharmacodynamic analyses, including: general summary statistics by visit, 11-KT/T ratio summaries by visit for males and females; and proportion of subjects with any reduction in 11-KT, a ≥ 50% reduction in 11-KT, and a normalization of 11-KT (11-KT ≤ ULN). 11-KT assessments, however, will not be provided to Spruce for this study. There are no standard assay or normal references of 11-KT for children. In addition, developing and validating an assay could not be completed in time for this study. Therefore, any protocol specified pharmacodynamic and exploratory endpoints for 11-KT will not be performed.

The Study Protocol Section 8.3.6 mentions that exploratory endpoint of the proportion of subjects with baseline dosing > 3 × daily who decrease frequency of administration ≤ 3 × daily. Given that the dose frequency is collected in a free text form in the Concomitant Medication eCRF form, the dose frequencies are not standardized and easily analyzable, therefore GC medications will only be listed and not summarized to provide information supporting this exploratory endpoint.

The Study Protocol Section 8.3.4.1 states that "Using dosing data, estimates of exposure to tildacerfont will be summarized." However, due to limitations in the collection of exposure and drug accountability data in this study, it is not possible to estimate tildacerfont exposure without making assumptions about the last dose date of the 12-week treatment period, the number of tablets dispensed, and the strength of the tablets dispensed. Therefore, information about exposure will only be listed on an individual basis as described in Section 12.1.

16 REFERENCES

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. (1996). *Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3).* Rockville, MD: Federal Register.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. (1998). *Guideline for Industry: Statistical Principles for Clinical Trials (ICH E9).* Rockville, MD: Federal Register.

17 APPENDIX A: SCHEDULE OF EVENTS

Table 8 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 every 6 months.

[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.

Table 9 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	
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

Table 10 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]
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					

	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
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 every 6 months.

[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.

Table 11 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		
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).

18 APPENDIX B: CLINICAL LABORATORY TESTS

Table 12 Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Potassium	Platelet count	Specific gravity
Calcium	RBC count	pH
Sodium	MCV	Glucose
BUN	MCH	Protein
Creatinine	% Reticulocytes	Blood
Total protein	Hemoglobin	Ketones
ALP	Hematocrit	Bilirubin
ALT/SGPT	WBC count	Urobilinogen
AST/SGOT	Neutrophils	Nitrate by dipstick
GGT	Lymphocytes	Microscopic examination
Total bilirubin	Monocytes	(if blood or protein is abnormal)
Direct bilirubin	Eosinophils	
Total bile acids	Basophils	
Coagulation	**Thyroid**	**Other**
PT	T3 (free and total)	11-KT
PTT	T4 (free and total)	17-OHP
INR	TSH	A4
		ACTH
		Testosterone

Abbreviations: 11-KT = 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; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cells

19 APPENDIX C: TILDACERFONT DOSE LEVELS AND PEDIATRIC WEIGHT-BASED DOSING

Table 13 Tildacerfont Dose Levels and Pediatric Weight-Based Dosing

Weight	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	200	300
≥ 33.9	50	100	150	200	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

20 APPENDIX D: PROHIBITED AND CAUTIONARY 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 Medical Monitor.

Table 14 Prohibited and Cautionary Concomitant Medications

alfentanil	apixaban	atorvastatin	avanafil	avasimibe
buspirone	carbamazepine	cenobamate	ciprofloxacin	darifenacin
diltiazem	elagolix	eletriptan	ethinyl estradiol (>35 µg)	felodipine
fluconazole	glyburide	isavuconazole	itraconazole	ketoconazole
lesinurad	loperamide	lovastatin	mibefradil	midazolam
nefazodone	oseltamivir	paxlovid [1]	phenobarbital	phenytoin
posaconazole	pravastatin	quetiapine	repaglinide	rifampin
rifapentine	rivaroxaban	sildenafil	simvastatin	St John's wort
teneligliptin	ticagrelor	triazolam	vardenafil	voriconazole

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