A Randomized, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety and Efficacy of Tildacerfont in Adult Subjects with Polycystic Ovary Syndrome (PCOS) and Elevated Adrenal Androgens

US IND Number:	154946
Study Number:	SPR001-210
Document Type:	Clinical study protocol
Protocol Version:	6.1 (supersedes Protocol dated 17 October 2022)
Protocol Date:	28 November 2022
Investigational Medicinal Product:	SPR001 (tildacerfont)
Indication:	Polycystic Ovary Syndrome (PCOS)
Sponsor:	Spruce Biosciences, Inc. 2001 Junipero Serra Blvd, Suite 640 Daly City, CA 94014
Registries:	ClinicalTrials.gov: NCT05370521

SPONSOR APPROVAL PAGE

A Randomized, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety and Efficacy of Tildacerfont in Adult Subjects with Polycystic Ovary Syndrome (PCOS) and Elevated Adrenal Androgens

Study Number: SPR001-210
Protocol Version: 6.1
Protocol Date: 28 November 2022

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

DocuSigned by:
Will Charlton MD
41EB0D56E6FF4EF...

12/7/2022

Will Charlton, MD
Chief Medical Officer

Date

DocuSigned by:
Vaeling Miller
C027BD1B9501453...

12/6/2022

Vaeling Miller
Vice President, Clinical Development Operations

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Randomized, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety and Efficacy of Tildacerfont in Adult Subjects with Polycystic Ovary Syndrome (PCOS) and Elevated Adrenal Androgens

Study Number: SPR001-210
Protocol Version: 6.1
Protocol Date: 28 November 2022

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

Site Name: _____

Principal Investigator Name: _____

_____ _____

Principal Investigator's Signature **Date**

PROTOCOL SYNOPSIS

Sponsor: Spruce Biosciences

Study Title: A Randomized, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety and Efficacy of Tildacerfont in Adult Subjects with Polycystic Ovary Syndrome (PCOS) and Elevated Adrenal Androgens

Protocol Number: SPR001-210 | **Phase:** 2

Objectives	Endpoints
Primary	
To evaluate the effect of tildacerfont in reducing dehydroepiandrosterone sulfate (DHEAS) in subjects with PCOS and elevated adrenal androgens	Absolute change from baseline in DHEAS
Secondary	
To evaluate the effect of tildacerfont in achieving target reduction in DHEAS in subjects with PCOS and elevated adrenal androgens	Proportion of subjects with: • ≥ 30% reduction from baseline in DHEAS • DHEAS ≤ upper limit of normal (ULN)
To evaluate the safety of tildacerfont in subjects with PCOS and elevated adrenal androgens	Adverse events (AEs), serious adverse events (SAEs)
Exploratory	
To evaluate the effect of tildacerfont in reducing key serum hormones and androgens in subjects with PCOS and elevated adrenal androgens	• Adrenocorticotropic hormone (ACTH) • Dehydroepiandrosterone (DHEA) • Total testosterone (T) • Androstenedione (A4) • 17-hydroxyprogesterone (17-OHP) • 11β-hydroxyandrostenedione (11OHA4) • 11β-hydroxytestosterone (11OHT) • 11-ketoandrostenedione (11KA4) • 11-ketotestosterone (11KT)

Study Design:

This is a randomized, placebo-controlled dose escalation study that will evaluate the safety and efficacy of 3 tildacerfont dose levels (50 mg, 100 mg, and 200 mg QD) compared to placebo for up to 12 weeks of treatment in subjects with PCOS and elevated adrenal androgens at baseline. The study is planned as a 3-period study with a duration of 4 weeks for each period.

The Schedule of Activities is provided in Section 12.2.

Subjects diagnosed with PCOS per the 1990 NIH criteria (Zawadski and Dunaif, 1992) will be screened to determine eligibility for the study over up to 2 screening visits. For subjects with unknown DHEAS elevations (within 6 months of target randomization date), an optional DHEAS Screening Visit may be used to test DHEAS level prior to further screening evaluations. In order to qualify for the study, a subject's DHEAS value must exceed the age-matched, reference ULN threshold. Screening Visit assessments will include safety laboratories and assessments. Subjects meeting all eligibility criteria will be randomized to either dose escalation with tildacerfont or matching placebo.

Subjects randomized to the tildacerfont group will initiate treatment with 4 weeks of 50 mg QD, then proceed to 4 weeks at 100 mg QD and complete the study with 4 weeks at 200 mg QD. All placebo subjects will remain on placebo over the full 12-week treatment period.

If signs, symptoms or biochemical evidence of adrenal insufficiency are noted, study drug will be suspended until adrenal function may be fully evaluated for relationship to clinical findings. If adrenal insufficiency is confirmed, study drug will be permanently discontinued.

Study drug will be administered at home during each period with an evening meal that should contain approximately <50% fat content.

Efficacy Assessments

Blood samples will be collected at every clinic visit for measurement of serum DHEAS levels.

Safety Assessments

Safety assessments will include monitoring and recording all AEs (including SAEs, AEs leading to discontinuation/withdrawal, and AESIs), physical examination, vital signs assessment, ECGs, clinical laboratories, including serum cortisol, and monitoring for suicide risk using the Columbia-Suicide Severity Rating Scale (C-SSRS).

PK Assessments

PK assessments will be conducted at Weeks 4, 8, and 12 and will consist of a single sample at 8 A.M. (± 1 hour).

Study Conduct:

Each subject's course will consist of the following visits:

Clinic Visits

Clinic visits will occur at the following times:

- Optional DHEAS Screening Visit
- Screening Visit (Safety labs and assessments, inclusion/exclusion criteria evaluation, medical history, and concomitant medications)
- Treatment Period:
  - Period 1: At Day 1 and Day 28
  - Period 2: Day 56
  - Period 3: Day 84
- Follow-up: At 30 days after the last dose of study drug

Clinic visits should be scheduled for the early morning, to accommodate morning laboratory assessments (approximately 8 A.M. ± 1 hour). DHEAS is expected to peak in the morning after overnight ACTH surge, so morning draws are optimal for the DHEAS Screening Visit. However, any previously documented DHEAS elevation will confirm eligibility during the optional pre-screening visit.

Telephone Contacts

Sites will make scheduled telephone contacts to all subjects at Weeks 2, 6, and 10 to assess for the occurrence of AEs and the initiation of new concomitant medications.

Subjects should be instructed to telephone sites if they have any concerns about their health and/or to report AEs.

Duration of Subject Participation: Approximately 25 weeks, inclusive of up to 30 days of optional DHEAS screening, 30 days of screening, 12 weeks of treatment, and 30 day follow up.

Planned Sample Size and Number of Sites: This study will enroll approximately 40 subjects at approximately 15 investigative sites within North America.

Study Drug and Route of Administration: Tildacerfont, an oral small-molecule corticotropin-releasing factor type-1 (CRF_1) receptor antagonist will be supplied as 50 mg tablets. Placebo will be supplied as tablets that look identical to drug product but contain no drug substance.

Subject Population: Female subjects 18 to 40 years old with PCOS and screening DHEAS levels that exceed the age-matched reference ULN threshold.

Criteria for Inclusion:

1. Female subjects, 18 to 40 years old, at the Screening Visit
2. Diagnosis of PCOS (either historical or during screening) according to the NIH (1990) criteria (Zawadski and Dunaif, 1992) (both (a) and (b) are necessary and other disorders causing hyperandrogenism and anovulation must be excluded):
   a. Presence of clinical and/or biochemical hyperandrogenism
   b. Chronic anovulation (defined as <8 menstrual cycles in the previous 12 months)
3. DHEAS level > age-matched reference ULN at the Screening Visit
4. Agrees to follow contraception guidelines (Section 4.2.4). Subjects must be postmenopausal, have documentation of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, be sexually abstinent, have a male sexual partner who is vasectomized, or agree to use a highly effective contraceptive method from at least 1 month before Screening until 30 days after the last dose of study drug.
5. Is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Criteria for Exclusion:

1. Evidence of any of the following:
   a. History of congenital adrenal hyperplasia, Cushing's syndrome, pituitary or adrenal disease
   b. Clinically significant hyperprolactinemia
   c. Thyroid stimulating hormone (TSH) <0.1 mU/mL or >4.5 mU/mL at screening
      i. Subjects receiving concomitant treatment for thyroid disease must be on stable medication for at least 6 weeks
   d. Cortisol levels concerning for adrenal insufficiency (A.M. basal cortisol level < 6.2 µg/dL at Screening
   e. Any other findings suggestive of a secondary cause for anovulation and/or hyperandrogenemia

2. Total testosterone levels >140 ng/dL, DHEAS >650 mcg/dL, virilization or other signs or symptoms concerning for ovarian hyperthecosis or androgen-secreting tumors
3. Medical conditions that require glucocorticoid treatment within 30 days of screening and throughout the duration of the study
4. Prior hysterectomy or bilateral oophorectomy
5. History of allergy or hypersensitivity to tildacerfont, any of its excipients, or any other CRF_1 receptor antagonist
6. A clinically significant unstable medical condition, medically significant illness, or chronic disease occurring during or within 30 days of screening, including but not limited to:
    a. An ongoing malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
    b. Estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m^2
    c. Current or history of liver disease (except Gilbert's syndrome)
    d. History of alcohol or substance abuse within the last year, or any significant history of alcohol or substance abuse that would likely prevent the subject from reliably participating in the study, based on the opinion of the Investigator
    e. Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV) at screening or other condition/therapy rendering a subject immunosuppressed during screening or throughout the duration of the study
    f. Subjects who plan to undergo bariatric surgery during the study are excluded.
7. Psychiatric conditions including, but not limited to bipolar, schizophrenia, or schizoaffective disorders that are not effectively controlled on medication and may, in the opinion of the Investigator, have adverse impact on study compliance. Symptoms of hallucinations, delusions and psychosis are exclusionary. Additionally:
    a. Increased risk of suicide based on the Investigator's judgment or the results of the Columbia–Suicide Severity Rating Scale (C-SSRS) conducted at screening (eg, C-SSRS Type 3, 4, or 5 ideation within the past 6 months or any suicidal behavior within the past 12 months)
8. Has clinically significant abnormal electrocardiogram (ECG) or clinical laboratory results during screening. Abnormal results that must be reviewed and discussed with the Medical Monitor to determine eligibility include but are not limited to:
    a. Any clinically meaningful abnormal ECG results, including Fridericia-corrected QT interval (QTcF) >470 ms
    b. Alanine aminotransferase (ALT) >2x ULN
    c. Total bilirubin >1.5x ULN
    d. Total bile acids >5x ULN
9. Is pregnant or nursing, or plans to become pregnant from screening until 30 days after the last dose of study drug
10. Use of any other investigational drug or device from 30 days or 5 half-lives (whichever is longer) before screening to the end of the study
11. Use of the following drugs or devices from 30 days or 5 half-lives (whichever is longer) before Day 1 to the end of the study:

a. Any medication for the treatment of PCOS including but not limited to antiandrogens, metformin, GnRH agonists, or other therapy or supplement that could impact subject safety or confound study data
b. Drugs which are or contain:
    i. Moderate to strong inhibitors and/or inducers of cytochrome P450 3A4 (CYP3A4)
    ii. Sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 (except hormonal contraception containing ≤35 µg ethinyl estradiol)
    iii. Sensitive substrates or narrow-therapeutic-range substrates of breast cancer resistance protein (BCRP) other than those which can be administered once-daily in the morning (separated by approximately 10 hours from study drug evening administration)

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

Safety Assessments: Safety assessments will include monitoring and recording all AEs, ECGs, clinical laboratories, and serum cortisol levels.

Efficacy Assessments: Blood samples will be collected at every visit for measurement of serum DHEAS levels**.**

Pharmacokinetic Assessments and Sampling: Pharmacokinetic assessments will be conducted at Weeks 4, 8, and 12 and will include a single sample.

Statistical Methods:

Statistical Hypotheses

Efficacy endpoints will be evaluated using the following hypothesis-testing schema: Each tildacerfont dose will be compared with placebo. The null hypothesis will be that there is no difference in the endpoint between a given dose level of tildacerfont and placebo. The alternative hypothesis will be that there is a difference.

Sample Size

A sample size of 33 subjects with 2:1 randomization will provide at least 80% power to detect a difference of 164 mcg/dL in mean DHEAS between at least one dose of tildacerfont and placebo assuming a standard deviation of 154 mcg/dL and a two-sided alpha of 0.05. Accounting for a 15% drop out, the final sample size is N=39 (n=26 for tildacerfont group and n=13 for placebo).

Subjects will be randomized using the strata of Screening DHEAS (≤1.2x ULN, >1.2x ULN).

Analysis Populations

- The Intent-to-Treat (ITT) Population will include all subjects randomized in the study.
- The modified Intent-to-Treat (mITT) Population will include subjects in the ITT Population who have at least one dose of study drug, a baseline DHEAS assessment and at least one post baseline DHEAS assessment.
- The Safety Population will include all subjects who receive at least 1 dose of study drug in the study.

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

Efficacy Analyses

All efficacy analyses will be conducted on mITT Population using a 2-sided alpha of 0.05. No adjustment for multiplicity is planned as this study is exploratory in nature.

The primary endpoint, the change from baseline in DHEAS, will be used to evaluate the preliminary efficacy of tildacerfont therapy relative to placebo and will be summarized using an analysis of covariance model (ANCOVA) with baseline DHEAS as a covariate and randomization strata and dose level as independent variables. Additional covariates may be added in the statistical analysis plan. The proportion of subjects meeting specific DHEAS thresholds will be summarized using exact tests through logistic regression using the randomization strata and dose level.

Exploratory hormone/androgen change endpoints will be analyzed using a similar methodology as the primary endpoint.

Safety Analyses

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

References: Zawadski JK and Dunaif A. Diagnostic criteria for polycystic ovary syndrome: Towards a rational approach. In: Polycystic Ovary Syndrome (Current Issues in Endocrinology and Metabolism), Dunaif A, Givens JR, Haseltine FP, Merriam GE (Eds), Blackwell Scientific Inc, Boston 1992. p.377.

TABLE OF CONTENTS

SPONSOR APPROVAL PAGE 2
INVESTIGATOR PROTOCOL AGREEMENT PAGE 3
PROTOCOL SYNOPSIS 4
TABLE OF CONTENTS 10
LIST OF TABLES 15
LIST OF FIGURES 15
LIST OF ABBREVIATIONS 16
1. INTRODUCTION 19
1.1. Background 19
1.1.1. Polycystic Ovary Syndrome 19
1.1.2. Current Treatment for PCOS 19
1.1.2.1. Diagnosis 20
1.1.3. Tildacerfont for the Treatment of PCOS 21
1.2. Study Rationale 21
1.2.1. Rationale for the Study Design 21
1.2.2. Rationale for Study Drug Dosing 22
1.3. Risk/Benefit Assessment 22
2. OBJECTIVES AND ENDPOINTS 24
3. STUDY DESIGN 25
3.1. Overall Design 25
3.1.1. Dose Escalation 25
3.1.2. Study Visits 26
3.1.2.1. DHEAS Screening Visit (Optional) 26
3.1.2.2. Screening Visit 26
3.1.2.3. Day 1 26
3.1.2.4. Treatment Periods 26
3.1.2.5. Follow-up Visit 27
3.1.2.6. Early Termination Visit 27
3.1.3. End of Study Definition 27
4. STUDY POPULATION 28

4.1. Eligibility Criteria 28
4.1.1. Inclusion Criteria 28
4.1.2. Exclusion Criteria 28
4.2. Lifestyle Considerations 30
4.2.1. Meals and Dietary Restrictions 30
4.2.2. Caffeine, Alcohol, and Tobacco 30
4.2.3. Activity 31
4.2.4. Contraception Guidelines 31
4.3. Screen Failures 32
5. STUDY TREATMENT 33
5.1. Treatment Administration 33
5.2. Preparation/Handling/Storage/Accountability 33
5.2.1. Acquisition and Accountability 33
5.2.2. Formulation, Appearance, Packaging, and Labeling 33
5.2.3. Product Storage 33
5.3. Treatment Assignment 34
5.4. Blinding 34
5.5. Study Intervention Compliance 34
5.6. Concomitant Therapy 34
5.6.1. Prohibited Concomitant Medications 35
6. STUDY DRUG DISCONTINUATION AND PARTICIPANT WITHDRAWAL 36
6.1. Study Drug Discontinuation 36
6.1.1. Dose-Limiting Toxicity Stopping Criteria 36
6.1.2. Safety Monitoring and Stopping Rules for Abnormal Liver Chemistry Measurements 36
6.1.3. QT Stopping Criteria 39
6.1.4. Suicidality Stopping Criteria 39
6.1.5. Depression or Anxiety Stopping Criteria 39
6.1.6. Adrenal Insufficiency Stopping Criteria 39
6.1.7. Reproductive Hormone Stopping Criteria 41
6.1.8. Platelet Stopping Criteria 41

6.1.9. Study Stopping Criteria 41
6.1.10. Clinically Significant Adverse Events 42
6.2. Subject Withdrawal from the Study 42
6.3. Lost to Follow-up 42
7. STUDY ASSESSMENTS AND PROCEDURES 44
7.1. Safety Assessments 44
7.1.1. Physical Examination 44
7.1.2. Vital Signs 44
7.1.3. Body Weight and Height 44
7.1.4. Electrocardiogram 44
7.1.5. Clinical Laboratories 45
7.1.6. Psychiatric Evaluations 45
7.1.6.1. Columbia-Suicide Severity Rating Scale (C-SSRS) 45
7.2. Adverse Events and Serious Adverse Events 46
7.2.1. Definition of Adverse Event 46
7.2.2. Definition of Serious Adverse Event 47
7.2.3. Classification of an Adverse Event 48
7.2.3.1. Severity 48
7.2.3.2. Relationship to Study Drug 48
7.2.3.3. Action Taken 50
7.2.3.4. Outcome 50
7.2.4. Time Period and Frequency for Event Assessment and Follow-up 50
7.2.5. Adverse Event Reporting 51
7.2.6. Serious Adverse Event Reporting 51
7.2.7. Reporting of Pregnancy 51
7.2.8. Adverse Events of Special Interest 52
7.2.9. Safety Oversight 53
7.3. Efficacy Assessments 53
7.4. Pharmacokinetic Assessments 53
8. STATISTICAL CONSIDERATIONS 54
8.1. Sample Size Determination 54

8.2. Populations for Analyses 54
8.3. Statistical Analyses....54
8.3.1. General Considerations 54
8.3.2. Demographics and Baseline Characteristics....54
8.3.3. Concomitant Medications 55
8.3.4. Efficacy Analyses....55
8.3.5. Safety Analyses 55
8.3.5.1. Extent of Exposure....55
8.3.5.2. Adverse Event Data....55
8.3.5.3. Clinical Laboratory Data....56
8.3.5.4. Vital Signs Data 56
8.3.5.5. Electrocardiogram Data....56
8.3.6. Pharmacokinetic Analyses 56
9. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS 57
9.1. Informed Consent 57
9.2. Study Discontinuation and Closure 57
9.3. Confidentiality and Privacy....57
9.4. Future Use of Stored Specimens and Data 58
9.5. Key Roles and Study Governance 58
9.5.1. Sponsor 58
9.5.2. Investigators 58
9.5.3. Institutional Review Board 58
9.6. Clinical Monitoring....58
9.7. Quality Assurance and Quality Control 59
9.8. Data Handling and Record Keeping 59
9.8.1. Data Collection and Management Responsibilities....59
9.8.2. Study Records Retention 59
9.9. Protocol Deviations....60
9.10. Publication and Data Sharing Policy....60
9.11. Amendments 61
10. COVID-19 RISK MITIGATION 62

10.1. Risk/Benefit Assessment in the Context of COVID-19....62
10.2. Study Conduct in the Context of COVID-19....62
10.3. Subject Disposition in the Context of COVID-19....62
10.4. Regulatory and Study Oversight Considerations in the Context of COVID-19....62
11. REFERENCES....63
12. APPENDICES....64
12.1. Optional DHEAS Screening Visit....64
12.2. Schedule of Activities....64
12.3. Appendix of Prohibited and Cautionary Concomitant Medications....68
12.4. Appendix of Clinical Laboratory Tests....69

LIST OF TABLES

Table 1. Therapies for PCOS in Adolescent and Adult Women 19
Table 2. Stopping Criteria and Increased Monitoring for Liver Chemistry Elevations 37
Table 3. Severity of Adverse Events.....48
Table 4. Relatedness of Adverse Event to Study Drug.....49
Table 5. Outcome of Adverse Events.....50

LIST OF FIGURES

Figure 1. Overall Study Design.....25

LIST OF ABBREVIATIONS

11KA4	11-ketoandrostenedione
11KT	11-ketotestosterone
11OHA4	11β-hydroxyandrostenedione
11OHT	11β-hydroxytestosterone
17-OHP	17-hydroxyprogesterone
A4	androstenedione
ACTH	adrenocorticotropic hormone, corticotropin
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
$AUC_{0\text{-}5hr}$	area under the plasma concentration vs time curve from time zero to 5 hours post-dose
BCRP	breast cancer resistance protein
BMI	body mass index
CAH	congenital adrenal hyperplasia
CBC	complete blood count
CNS	central nervous system
COC	combined oral contraception
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	corticotropin-releasing factor
CRF_1	corticotropin-releasing factor type-1
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulfate

DLT	dose-limiting toxicity
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HEENT	head, eyes, ears, neck, and throat
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	intrauterine system
LDL	low-density lipoprotein
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
NIH	National Institutes of Health
OTC	over-the-counter
PCOS	polycystic ovary syndrome

PK	pharmacokinetic(s)
Q1	25th percentile
Q3	75th percentile
QD	once daily
QTcF	Fridericia-corrected QT interval
SAE	serious adverse event
SAP	Statistical Analysis Plan
SHBG	sex hormone-binding globulin
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
T	testosterone
TEAE	treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background

1.1.1. Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder initially described in the mid-1930s that now affects up to 12% of reproductive aged women in the U.S. (CDC, 2020) and is the most frequent cause of female infertility (Mohammad, 2017). Heterogeneous in nature, PCOS most commonly presents with hyperandrogenism (eg, hirsutism) and irregular menses with underlying ovulatory dysfunction resulting in subfertility or infertility (Mohammad, 2017). Hyperandrogenemia may be predominantly ovarian or adrenal in source; however, overlap is not uncommon (Rosenfield, 2011).

Though the pathophysiology of PCOS has not been fully elucidated, evidence suggests that while elevated levels and sensitivity to luteinizing hormone (LH) drives increased ovarian androgen production, adrenal androgen production results from hyperresponsiveness of the adrenal gland zona reticularis region to the adrenocorticotropic hormone (ACTH) signal from the anterior pituitary (Carmina, 1986; Swart, 2013).

In up to approximately 40% of patients with PCOS, adrenal hyperandrogenism is present, with or without ovarian hyperandrogenism (Rosenfield, 2016). Dehydroepiandrosterone sulfate (DHEAS) is an adrenal androgen that can serve as a biochemical marker for adrenal androgen overproduction.

1.1.2. Current Treatment for PCOS

Goals of PCOS therapy are multi-faceted and include not only alleviation of clinical signs of hyperandrogenism and contraception and/or fertility management, but also appropriate therapeutic screening and intervention of metabolic disorders that increase cardiovascular risk. A summary of these measures is provided below in Table 1.

Table 1. Therapies for PCOS in Adolescent and Adult Women

Therapies	Risks/Benefits
Lifestyle changes	• Weight loss via calorie restriction and exercise is recommended in both adolescents and adult women with a BMI ≥25 kg/m^2 • Offers potential metabolic, cardiac, and reproductive benefits

Therapies	Risks/Benefits
Insulin sensitizer (Metformin)	• Recommended for women with impaired glucose tolerance or type 2 diabetes in which lifestyle changes yielded insufficient results • An alternative therapy to treat irregular menses in patients who are intolerant of hormonal contraception • May be used to mitigate development of ovarian hyperstimulation syndrome when *in vitro* fertilization is used in patients with PCOS
Estrogen modulators	• 1st line treatment for infertility due to anovulation in PCOS
Hormonal contraception	• COC is the 1st line treatment in adolescents (including select premenarchal girls) and adults for hirsutism, acne, and menstrual irregularities or if applicable, to prevent conception granted individual risk-benefit assessment deems COC use is appropriate • Progestin exposure also offers protection against estrogen-mediated endometrial proliferation
Antiandrogens	• Typically used as an adjunct to COCs to treat hirsutism when COC response is insufficient • Monotherapy with antiandrogens may be indicated in patients who are intolerant of COCs or use is contraindicated, but adequate alternative contraception must be used due to fetal toxicity concerns

Abbreviations: BMI, body mass index; COC, combined oral contraception; PCOS, polycystic ovary syndrome

It is not uncommon for patients to require additional cosmetic measures in order to sufficiently manage hirsutism. These include hair removal via laser or mechanical means; topical eflornithine hydrochloride cream may also be used to inhibit hair growth but requires continuous use to remain effective.

1.1.2.1. Diagnosis

In this study, the modified National Institutes of Health (NIH) 1990 criteria (Zawadski and Dunaif, 1992) will be used for diagnosis, but will require evidence of adrenal-based hyperandrogenemia (DHEAS > age-matched upper limit of normal [ULN]). The NIH diagnostic criteria state that patients must satisfy both of the following criteria:

- Clinical and/or biochemical signs of hyperandrogenism
- Menstrual irregularity due to oligo- or anovulation

Other disorders causing hyperandrogenism and anovulation must be excluded.

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

1.1.3. Tildacerfont for the Treatment of PCOS

Tildacerfont is an oral small-molecule antagonist of the corticotropin-releasing factor (CRF) type-1 (CRF_1) receptor. In vitro studies show that tildacerfont binds to CRF_1 receptors with high affinity and specificity and blocks CRF-stimulated receptor function.

Tildacerfont has demonstrated the ability to reduce the levels of ACTH and downstream adrenal androgen production (17-hydroxyprogesterone [17-OHP] and androstenedione [A4]) in adult patients with CAH. While the etiology of adrenal androgen excess in PCOS is not fully understood, one hypothesis is that adrenal hyperandrogenemia is due to adrenal hyper-responsiveness to ACTH. Thus, tildacerfont's mechanism of action is well-suited to potentially reduce elevated adrenal androgen levels in PCOS patients who are biochemically hyperresponsive to ACTH by reducing ACTH and as a result, possibly improve clinical manifestations such as hirsutism, acne, irregular menses, and anovulation.

Non-clinical studies and clinical studies of tildacerfont are summarized in the IB.

1.2. Study Rationale

1.2.1. Rationale for the Study Design

The SPR001-210 study is a randomized, placebo-controlled, dose escalation study that will evaluate the preliminary efficacy and safety of tildacerfont (50 mg, 100 mg, and 200 mg once daily [QD]) compared to placebo after 12 weeks of double-blind treatment in subjects with PCOS and elevated adrenal androgens at baseline. Subjects randomized to the tildacerfont group will receive 3 escalating dose levels of tildacerfont with each dose level administered for 4 weeks. All subjects randomized to placebo will remain on placebo over the full 12-week treatment period. To be able to characterize changes and the magnitude of changes in DHEAS as due to treatment and to account for any inherent variability in DHEAS, a placebo treatment group is warranted. Four weeks of treatment was deemed minimally adequate to observe change in hormones and androgens, given the exposure profile of tildacerfont which achieves steady state after approximately 2 weeks of dosing.

DHEAS is the primary hormone being evaluated in this study and was selected as a stable biomarker of androgen production. Additionally, reduction in DHEAS was chosen as the efficacy endpoint as the vast majority (>90%) of DHEAS is produced in the adrenal glands and is therefore representative of an adrenal source of hyperandrogenemia, which is the population that may potentially be addressed with tildacerfont. The level of receptor occupancy necessary to result in reduction in DHEAS in subjects with PCOS is unknown. A dose of 50 mg is expected to result in ≤50% receptor occupancy while a dose of 200 mg is expected to provide ≥90% receptor occupancy. The range of doses was chosen to understand if increasing dose can provide additional reductions in DHEAS levels.

Additionally, the study will provide preliminary safety data over up to 12 weeks of treatment with tildacerfont in the PCOS population. Safety visits are planned every 4 weeks at the end of each treatment period at a dose level with a scheduled telephone call 2 weeks after initiating each tildacerfont dose level. The level of safety monitoring should provide adequate oversight

given the observed safety and tolerability profile to date. The study population will include women (18 to 40 years of age) with PCOS, characterized by the presence of hyperandrogenemia as indicated by a screening serum DHEAS level > age-matched reference ULN.

1.2.2. Rationale for Study Drug Dosing

Tildacerfont tablets will be administered starting at 50 mg and up to 200 mg QD. The long half-life of tildacerfont, approximately 60 hours after single-dose administration, supports QD dosing in this study.

The safety data from previous Phase 1 and Phase 2 studies show that tildacerfont at a dose of ≤200 mg/day has been generally well tolerated. The most common non-procedural adverse events (AEs) reported in completed studies, across all dose levels, were headache, diarrhea, constipation, nausea, and cough. No serious adverse events (SAEs) related to study drug have been observed to date.

In studies with CAH patients (n=26) with 2 to up to 12 weeks of treatment at total daily doses of ≥200 mg, the most common AEs were upper respiratory tract infection (n=4) and contusion, diarrhea, and headache (all n=3).

Healthy adult subjects have been dosed with similar amounts of tildacerfont (50 mg [n=8], 150 mg [n=9], and 200 mg QD [n=6]) for up to 14 days in a Phase 1 study. Tildacerfont did not produce a clinically significant change in ACTH levels in healthy subjects with normal baseline ACTH levels, nor change the 24-hour diurnal cortisol concentration profile, the cortisol area under the plasma concentration vs time curve from time zero to 5 hours post-dose ($AUC_{0\text{-}5hr}$) or affect the cortisol surge response to a hypoglycemic stressor (post an insulin tolerance test). Post insulin tolerance test cortisol profiles for tildacerfont treated subjects were indistinguishable from placebo with tildacerfont/placebo $AUC_{0\text{-}5hr}$ ratios from 1.13 to 1.19.

Additionally, no AEs of adrenal insufficiency have been noted in the completed studies to date.

The starting dose of 50 mg was based on the minimum level of CRF_1 receptor engagement reasonably expected to have an effect in patients with PCOS.

Given the observed safety profile to date, doses from 50 to 200 mg were deemed appropriate in this PCOS Investigational New Drug (IND) opening study.

1.3. Risk/Benefit Assessment

There exists an unmet need for disease-mitigating therapy in patients with PCOS, especially for those with disease refractory to current treatments.

Current therapies for PCOS are symptomatic in nature, and don’t differentiate between the unique sources of hyperandrogenemia. While there are several therapies available to treat PCOS, no therapies exist to treat adrenal androgen overproduction specifically. Availability of a therapy to reduce adrenal androgen production may provide a unique addition to the therapeutic choices for patients and physicians in addressing the clinical sequelae of this syndrome.

Potential risks of tildacerfont based on non-clinical studies include hepatotoxicity, developmental toxicity, male reproductive toxicity, thyroid toxicity, and prolongation of the QT interval. All were noted at exposures of tildacerfont that exceed clinical use. With the exception of reversible increases in liver transaminases, other non-clinical findings have not been appreciated in human subjects.

Tildacerfont is neither mutagenic nor clastogenic/aneugenic. There were no noteworthy adverse findings in fertility or embryo-fetal development studies in rats. In embryo-fetal development studies in rabbits, reductions in maternal weights and feed consumption were observed. Developmental toxicity, which occurred concomitantly with maternal toxicity, included resorptions and post implantation loss, reductions in litter sizes and live fetuses, lower fetal body weights and external, visceral and skeletal malformations. All were noted at exposures of tildacerfont that exceed clinical use (see the IB for details).

Tildacerfont is metabolized primarily by cytochrome P450 3A4 (CYP3A4); thus, drugs that are known moderate to strong inducers or inhibitors of CYP3A4 should be used with caution when co-administered with tildacerfont. Tildacerfont is a moderate inhibitor of the CYP3A4 pathway. Thus, dose reductions may be warranted for drugs which are sensitive or narrow-therapeutic-range substrates for CYP3A4. Caution may need to be exercised when co-administering tildacerfont with agents that are known substrates of breast cancer resistance protein (BCRP) or bile salt export pump.

In clinical trials, one subject had transaminase elevations of >3X ULN at 1000 mg QD. A second subject had a smaller elevation, <3X ULN, at the same dose level. The elevations resolved with discontinuation of tildacerfont and were not associated with bilirubin elevations. Additionally, the subject with the >3X ULN elevation had a smaller elevation at 400 mg QD (<3X ULN) that as associated with pruritus which resolved with discontinuation of tildacerfont and was not associated with bilirubin elevations.

Tildacerfont is expected to be generally well tolerated at doses ≤200 mg QD based on clinical data from healthy adults and subjects with CAH. The most common non-procedural AEs, across all dose levels, reported in completed studies were headache, diarrhea, constipation, nausea, and cough. No SAEs related to study drug have been observed. To date, there is no evidence of adrenal insufficiency in healthy subjects who have received tildacerfont.

The available benefit-to-risk assessment for tildacerfont warrants a Phase 2 study in subjects with PCOS.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the effect of tildacerfont in reducing DHEAS in subjects with PCOS and elevated adrenal androgens	Absolute change from baseline in DHEAS
Secondary	
To evaluate the effect of tildacerfont in achieving target reductions in DHEAS in subjects with PCOS and elevated adrenal androgens	Proportion of subjects with: • ≥30% reduction from baseline in DHEAS • DHEAS ≤ ULN
To evaluate the safety of tildacerfont in subjects with PCOS with elevated adrenal androgens	• AEs and SAEs
Exploratory	
To evaluate the effect of tildacerfont in reducing key serum hormones and androgens in subjects with PCOS and elevated adrenal androgens	• ACTH • DHEA • T • A4 • 17-OHP • 11OHA4 • 11OHT • 11KA4 • 11KT

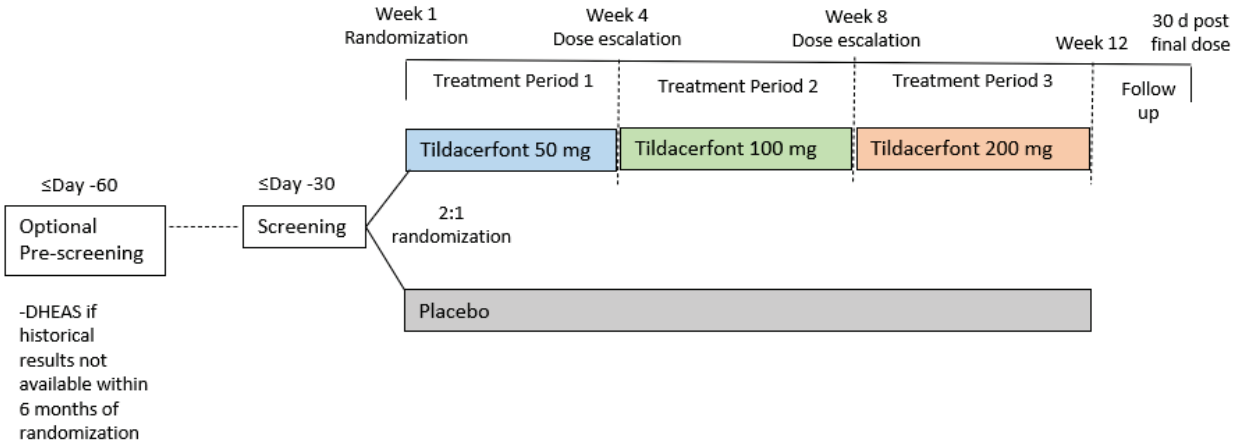
3. STUDY DESIGN

3.1. Overall Design

The SPR001-210 study is a randomized, placebo-controlled, dose escalation study that will evaluate the efficacy and safety of tildacerfont (50 mg, 100 mg, and 200 mg QD) compared to placebo after 12 weeks of double-blind treatment in subjects with PCOS and elevated adrenal androgens at baseline. Subjects randomized to the tildacerfont group will receive 3 escalating dose levels of tildacerfont with each dose level administered for 4 weeks. All placebo subjects will remain on placebo over the full 12-week treatment period. Subjects diagnosed with PCOS per the 1990 NIH criteria (Zawadski and Dunaif, 1992), will be screened to determine eligibility for the study over up to 2 screening visits (see Section 3.1.2.1). Subjects who continue to meet all eligibility criteria will be randomized to either dose escalation with tildacerfont or matching placebo in a 2:1 ratio.

A schema of the study design is presented in Figure 1.

Figure 1. Overall Study Design



Abbreviations: d, day; DHEAS, dehydroepiandrosterone sulfate.

3.1.1. Dose Escalation

Subjects randomized to the tildacerfont group will initiate treatment with 4 weeks of 50 mg QD, then proceed to 4 weeks at 100 mg QD and complete the study with 4 weeks at 200 mg QD. All placebo subjects will remain on placebo over the full 12-week treatment period. If signs, symptoms or biochemical evidence of adrenal insufficiency are noted, study drug will be suspended until adrenal function may be fully evaluated for relationship to clinical findings. If adrenal insufficiency is confirmed, study drug will be permanently discontinued and treatment will be managed by the Investigator according to standard medical practice. Complete stopping criteria for adrenal insufficiency are provided in Section 6.1.6.

3.1.2. Study Visits

Each subject will undergo a Screening Visit within 30 days of Day 1, three 4-week treatment periods, and a 30-day follow-up period. Subjects may also attend a DHEAS Screening Visit if needed (see Section 3.1.2.1). See the Schedule of Activities for full details of each study visit (Section 12.2).

Clinic visits should be scheduled for early in the morning to accommodate morning laboratory assessments (at 8 A.M. ± 1 hour).

Sites will make scheduled telephone contacts to all subjects at Weeks 2, 6, and 10 to assess for the occurrence of any AEs and the initiation of new concomitant medications. The Early Termination Visit/Follow-up Visit may also be conducted by telephone at the discretion of the Investigator.

Subjects should be instructed to telephone sites if they have any concerns about their health and/or to report AEs.

3.1.2.1. DHEAS Screening Visit (Optional)

For subjects with unknown DHEAS levels within 6 months of target randomization date, an optional DHEAS Screening Visit may be conducted up to 60 days prior to Day 1 to test DHEAS levels prior to further screening evaluations (see Section 12.1). An informed consent form (ICF) specific for this visit will be signed.

3.1.2.2. Screening Visit

See the Schedule of Activities (Section 12.2) for full details of assessments conducted at the Screening Visit.

3.1.2.3. Day 1

On Day 1, inclusion/exclusion criteria will be confirmed, and subjects will be randomized to treatment. A urinalysis, pregnancy test, physical examination, electrocardiogram (ECG), and pharmacokinetic (PK) sample will be conducted prior to the first dose administered. Study drug for Treatment Period 1 will be dispensed. Other assessments will be performed as detailed in the Schedule of Activities (Section 12.2).

3.1.2.4. Treatment Periods

Subjects will have 2 clinic visits in Treatment Period 1 (Weeks 1 and 4), and 1 clinic visit each in Treatment Periods 2 and 3 (Weeks 8 and 12, respectively).

At all clinic visits, including Day 1, concomitant medication and AE information will be reviewed. Vital signs and body weight will be measured. A pregnancy test, physical exam (either full or abbreviated), Columbia-Suicide Severity Rating Scale (C-SSRS), ECG, and 8 A.M. blood draw for PK will be conducted. Clinical laboratory and hormone assessments will be done, and A.M. serum cortisol will be collected. See Section 12.4 for details of clinical laboratory and hormone assessments.

Telephone contacts will be conducted at Weeks 2, 6, 10 for Treatment Periods 1, 2, 3, respectively.

Study drug will be dispensed for the next treatment period at Weeks 4 and 8.

3.1.2.5. Follow-up Visit

All subjects will return to the clinic (or, at the discretion of the Investigator, be contacted via telephone) for a final Follow-up Visit within 30 days after the last dose of study drug. Concomitant medication and AE information will be reviewed.

3.1.2.6. Early Termination Visit

Subjects who received any dose of study drug and discontinue study drug early or withdraw from the study will undergo an Early Termination Visit as soon as possible after the last dose of study drug. The Investigator will inquire about the reason for withdrawal and request the return of all unused study drug. Early termination assessments will occur as outlined in the Schedule of Activities (Section 12.2).

3.1.3. End of Study Definition

A subject is considered to have completed study treatment if they completed the Week 12 Visit. A subject is considered to have completed the study if the subject completes the Follow-up Visit. The end of the study is defined as the date of the last Follow-up Visit of the last subject in the study.

4. STUDY POPULATION

This study will enroll approximately 40 subjects aged 18-40 years with PCOS and evidence of excess adrenal androgens, randomized 2:1 to either tildacerfont or placebo. The study will be enrolled at up to approximately 15 investigative sites within North America.

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

4.1. Eligibility Criteria

4.1.1. Inclusion Criteria

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

1. Female subjects, 18 to 40 years old, at the Screening Visit
2. Diagnosis of PCOS (either historical or during screening) according to the NIH (1990) criteria (Zawadski and Dunaif, 1992) (both (a) and (b) are necessary and other disorders causing hyperandrogenism and anovulation must be excluded):

   (a) Presence of clinical and/or biochemical hyperandrogenism

   (b) Chronic anovulation (defined as <8 menstrual cycles in the previous 12 months)
3. DHEAS level > age-matched reference ULN at the Screening Visit
4. Agrees to follow contraception guidelines (Section 4.2.4).
5. Is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

4.1.2. Exclusion Criteria

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

1. Evidence of any of the following:
   a. History of congenital adrenal hyperplasia, Cushing's syndrome, pituitary or adrenal disease
   b. Clinically significant hyperprolactinemia
   c. Thyroid stimulating hormone (TSH) <0.1 mU/mL or >4.5 mU/mL at screening
      i. Subjects receiving concomitant treatment for thyroid disease must be on stable medication for at least 6 weeks
   d. Cortisol levels concerning for adrenal insufficiency (A.M. basal cortisol level <6.2 µg/dL at Screening

e. Any other findings suggestive of a secondary cause for anovulation and/or hyperandrogenemia

2. Total testosterone levels >140 ng/dL, DHEAS >650 mcg/dL, virilization or other signs or symptoms concerning for ovarian hyperthecosis or androgen-secreting tumors
3. Medical conditions that require glucocorticoid treatment within 30 days of screening and throughout the duration of the study
4. Prior hysterectomy or bilateral oophorectomy
5. History of allergy or hypersensitivity to tildacerfont, any of its excipients, or any other CRF_1 receptor antagonist
6. A clinically significant unstable medical condition, medically significant illness, or chronic disease occurring during or within 30 days of screening, including but not limited to:
   a. An ongoing malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
   b. Estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m^2
   c. Current history of liver disease (except Gilbert's syndrome)
   d. History of alcohol or substance abuse within the last year, or any significant history of alcohol or substance abuse that would likely prevent the subject from reliably participating in the study, based on the opinion of the Investigator
   e. Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV) at screening or other condition/therapy rendering a subject immunosuppressed during screening or throughout the duration of the study
   f. Subjects who plan to undergo bariatric surgery during the study are excluded.
7. Psychiatric conditions including, but not limited to bipolar, schizophrenia, or schizoaffective disorders that are not effectively controlled on medication and may have an adverse impact on study compliance. Symptoms of hallucinations, delusions and psychosis are exclusionary. Additionally:
   a. Increased risk of suicide based on the Investigator's judgment or the results of the C-SSRS conducted at screening (eg, C-SSRS Type 3, 4, or 5 ideation within the past 6 months or any suicidal behavior within the past 12 months)
8. Has clinically significant abnormal ECG or clinical laboratory results during screening. Abnormal results that must be reviewed and discussed with the Medical Monitor to determine eligibility include but are not limited to:
   a. Any clinically meaningful abnormal ECG results, including Fridericia-corrected QT interval (QTcF) >470 ms
   b. Alanine aminotransferase (ALT) >2x ULN
   c. Total bilirubin >1.5x ULN
   d. Total bile acids >5x ULN

9. Is pregnant or nursing, or plans to become pregnant from screening until 30 days after the last dose of study drug
10. Use of any other investigational drug or device from 30 days or 5 half-lives (whichever is longer) before screening to the end of the study
11. Use of the following drugs or devices from 30 days or 5 half-lives (whichever is longer) before Day 1 to the end of the study:
    a. Any medication for the treatment of PCOS including but not limited to antiandrogens, metformin, gonadotropin-releasing hormone (GnRH) agonists, or other therapy or supplement that could impact subject safety or confound study data
    b. Drugs which are or contain:
        i. Moderate to strong inhibitors and/or inducers of CYP3A4
        ii. Sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 (except hormonal contraception containing ≤35 µg ethinyl estradiol)
        iii. Sensitive substrates or narrow-therapeutic-range substrates of BCRP other than those which can be administered once-daily in the morning (separated by approximately 10 hours from study drug evening administration)

        Refer to Appendix 12.3 for a list of prohibited and cautionary concomitant medications.
12. Donation or receipt of blood from 90 days before screening to the end of the study; or donation or receipt of platelets, white blood cells, or plasma from 30 days prior to screening to the end of the study

4.2. Lifestyle Considerations

4.2.1. Meals and Dietary Restrictions

Study drug must be consumed with food. Study drug will be consumed with an evening meal that should contain <50% fat content. Study drug may be consumed up to 30 minutes after completing the evening meal, if necessary. If a subject has not consumed study drug within 30 minutes after the evening meal, the subject should consume study drug with a snack containing <50% fat content. Study drug will be consumed before midnight.

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

4.2.2. Caffeine, Alcohol, and Tobacco

For study visits with blood draws, subjects should abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, or chocolate) within 5 hours before the blood draw (after 3 A.M.). Subjects will abstain from imbibing alcohol within 12 hours before the blood draw (after 8 P.M.).

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

4.2.3. Activity

Subjects should abstain from strenuous exercise for 8 hours before each study visit. Strenuous exercise might cause temporary spikes in biomarkers that could confound analysis of the effect of study drug. Subjects should not exercise within 30 minutes before any study-related procedure.

4.2.4. Contraception Guidelines

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

1. Is postmenopausal at Screening

   A postmenopausal state is defined as no menses for at least 1 year without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, a single FSH measurement is insufficient to establish a postmenopausal state without at least 1 year of amenorrhea.
2. Has documentation of one of the following performed before Screening:
   a. Hysterectomy
   b. Bilateral salpingectomy
   c. Bilateral oophorectomy
3. Is sexually abstinent from penile-vaginal intercourse as her usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent from Screening until 30 days after the last dose of study drug
4. Any male sexual partner is vasectomized, and the absence of sperm has been confirmed
5. Agrees to use one of the following highly effective contraceptive methods, which must be in place from at least 1 month before Screening until 30 days after the last dose of study drug:
   a. Combined hormonal contraception (containing estrogen and progestogen) associated with inhibition of ovulation: oral, intravaginal, or transdermal

      Any hormonal contraception containing ethinyl estradiol must contain ≤35 µg ethinyl estradiol, is permitted only for subjects who would not be considered at high risk for thromboembolic or cardiovascular complications with estrogen use, and must be used simultaneously with a backup method of contraception. Acceptable backup methods of contraception include diaphragm with spermicide, cervical cap with spermicide, vaginal sponge with spermicide, and male or female condom with or without spermicide. Dosing of oral formulations of hormonal contraception containing ethinyl estradiol should be offset by approximately 10 hours from the

evening dose of study drug. The Investigator may consult with the Medical Monitor regarding such individuals.

b. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
c. Intrauterine device (IUD)
d. Intrauterine system (IUS)
e. Bilateral tubal occlusion

4.3. Screen Failures

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

Individuals who do not meet the preceding criteria for participation in the study may be rescreened according to the following guidelines. The Investigator will first consult with the Medical Monitor regarding such individuals.

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

5. STUDY TREATMENT

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

5.1. Treatment Administration

All subjects will be treated with 3 doses of oral tildacerfont (50 mg, 100 mg, or 200 mg QD), or placebo for 12 weeks.

Study drug will be taken with the subject's evening meal (see Section 4.2.1) between 6 P.M. and midnight.

Study drug will be dispensed at Day 1, Week 4, and Week 8. Only authorized study staff may dispense study drug. Sites will provide subjects with dosing instructions.

Criteria for study drug discontinuation are provided in Section 6.1.

5.2. Preparation/Handling/Storage/Accountability

5.2.1. Acquisition and Accountability

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

5.2.2. Formulation, Appearance, Packaging, and Labeling

The drug product tildacerfont (SPR001) is formulated as a tablet containing 50 mg of drug substance. Tildacerfont tablets are round and convex in shape and yellow in color and will be packaged into blister cards.

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

All study treatment packaging (both drug product and placebo) will be labeled with the protocol number, recommended storage conditions, name and address of the Sponsor, an Investigational Use Statement (eg, "Caution: New Drug – Limited by Federal [USA] Law to Investigational Use"), and the instruction that the agent should be kept out of the reach of children. Labeling will comply with all legal requirements and supply no information about individual subjects.

5.2.3. Product Storage

All study drug should be stored at room temperature (25°C [77°F], excursions between 15°C to 30°C [59°F to 86°F] are permitted). Study drug must be stored in a secure, environmentally controlled area that is monitored (manually or automatically) and accessible only to the Investigator and authorized study staff. For additional information on product storage, please refer to the Pharmacy Manual.

5.3. Treatment Assignment

Subjects will be randomized to either dose escalation with tildacerfont or matching placebo in a 2:1 ratio. Subjects will be randomized using the strata of Screening DHEAS (≤1.2x ULN, >1.2x ULN).

Subjects randomized to the tildacerfont group in Treatment Period 1 will receive 50 mg QD for 4 weeks, escalate to 100 mg QD for 4 weeks in Treatment Period 2, and escalate to 200 mg QD for 4 weeks in Treatment Period 3. All placebo subjects will remain on placebo over the full 12-week treatment period.

5.4. Blinding

Subjects, Investigators, Sponsor study team, and all site personnel will be blinded to study drug.

Tildacerfont and matching placebo tablets will be packaged the same and will be identical in appearance and taste.

Randomization and trial supply management will be managed though an Interactive Response Technology (IRT) system and will be used to assign a treatment to subjects who meet eligibility criteria. The IRT is used to control all drug distribution and inventory for this study. The IRT will be responsible for subsequent issue of treatment kits, as appropriate to the visit schedule.

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

5.5. Study Intervention Compliance

Study drug will be returned for accountability at Week 4, Week 8, and Week 12. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol.

5.6. Concomitant Therapy

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

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

All concomitant medications should be compared against the list of prohibited medications and the list of other medications of concern provided in Section 12.3. Subjects should be instructed to contact the site immediately any time a new medication is required during the course of the

study, including prescription and OTC medications, even those to be used for only a short period of time (eg, antibiotics, cold and flu remedies, gastrointestinal [GI] therapies, opioids or other pain relievers). The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

5.6.1. Prohibited Concomitant Medications

- Use of other investigational drugs including GnRH agonists and antagonists, metformin and anti-androgens (spironolactone), as well as investigational devices are prohibited during the study
- Rosiglitazone, aromatase inhibitors, testosterone, growth hormones or any other medication or supplement that could impact subject safety or confound interpretation of study results are prohibited
- Moderate to strong inhibitors and/or inducers of CYP3A4; this includes consumption of grapefruit, grapefruit juice, or any foods that are known to be strong CYP3A4 inhibitors from 1 day before the first dose of study drug until after the final dose
- Sensitive substrates or narrow-therapeutic-range substrates of CYP3A4 (eg, oxycodone)
- Ethinyl estradiol >35 µg
- Sensitive substrates or narrow-therapeutic-range substrates of BCRP (except those that can be administered QD in the morning, separated by approximately 10 hours from evening administration of study drug)

Appendix 12.3 provides a non-exhaustive list of medications, including many commonly used medications, that are prohibited because of their potential for metabolic interactions with tildacerfont. It is critical that each subject's concomitant medications are carefully compared to the list in Appendix 12.3.

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

6. STUDY DRUG DISCONTINUATION AND PARTICIPANT WITHDRAWAL

6.1. Study Drug Discontinuation

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

If study drug is discontinued, the Investigator will report the discontinuation to the Medical Monitor, document the date and reason for study drug discontinuation on the appropriate electronic case report form (eCRF), schedule an Early Termination Visit for the subject as soon as possible (see the Schedule of Activities in Section 12.2), provide or arrange for appropriate follow-up, and document the course of the subject's condition.

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

6.1.1. Dose-Limiting Toxicity Stopping Criteria

A dose-limiting toxicity (DLT) is defined as a Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher treatment-emergent AE (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 Section 6.1.9).

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

The criteria in Table 2 were adapted in accordance with the non-binding recommendations contained within the Food and Drug Administration (FDA) Guidance for Industry Drug-Induced Liver Injury: Pre-marketing Clinical Evaluation, from the U.S. Department of Health and Human Services in July 2009.

Although there is no reasonable expectation that study drug exposure of ≤200 mg QD will result in hepatic toxicity, out of an abundance of caution in this study, abnormal transaminase results will be assessed as follows.

If stopping criteria are met at any time during the Treatment Period, study drug should be held until confirmatory testing of the transaminase, with additional measurements of total bilirubin, alkaline phosphatase, complete blood count (CBC), and international normalized ratio (INR) is performed and be reported as an adverse event of special interest (AESI). Ideally, confirmatory testing would be performed within 48-72 hours of the initial receipt of the abnormal result. Confirmation testing through the central lab is preferred, but local laboratory testing may be necessary in certain circumstances. In cases where a possible Hy's Law case is present or any

other seriousness criteria are met, this should be reported as a SAE and AESI. Table 2 outlines specific stopping criteria for this study.

Table 2. Stopping Criteria and Increased Monitoring for Liver Chemistry Elevations

Criteria	Actions
Appearance of fatigue, nausea, vomiting right upper quadrant pain or tenderness, fever, jaundice, rash and/or eosinophilia (>5%) believed to be related to liver injury or hypersensitivity.	Hold study drug, measure liver chemistry (AST/ALT/ALP), total bilirubin, total bile acids, CBC with differential and INR within 48-72 hours and notify Sponsor.
ALT or AST ≥ 5x ULN	Discontinue study drug and notify Sponsor. Follow the protocol's **Laboratory Monitoring of Liver Function**.
ALT ≥ 3x ULN	**Treatment Periods 1 and 2:** a. Monitor liver chemistry (AST/ALT/ALP), total bilirubin, total bile acids, CBC with differential and INR within 48-72 hours and notify Sponsor b. If no other stopping criteria are met, monitor AST/ALT/ALP and INR 2x weekly for the remainder of the current treatment period (may be performed weekly if AST/ALT stabilizes and the subject is asymptomatic) while continuing study drug c. If ALT >3x ULN at the conclusion of the current treatment period, withdraw the subject from the study **Treatment Period 3:** a. Follow the same notification and monitoring instructions detailed in (a) and (b) above for Treatment Periods 1 and 2. b. If ALT >3x ULN persists for 4 weeks, discontinue study drug and notify Sponsor

Criteria		Actions
ALT ≥ 3x ULN	AND total bilirubin ≥ 2x ULN (>35% direct bilirubin)[1]	Discontinue study drug and notify Sponsor. Possible Hy's Law case—**report as SAE and AESI**
	AND INR >1.5	Discontinue study drug and notify Sponsor. Possible Hy's Law case—**report as SAE and AESI**
	AND total bile acids>3x ULN	Hold study drug and notify Sponsor. Measure liver chemistry (AST/ALT/ALP), total bilirubin, total bile acids, CBC with differential and INR within 48-72 hours and discuss with Medical Monitor whether to discontinue study drug.
	AND the appearance of fatigue, nausea, vomiting right upper quadrant pain or tenderness, jaundice, fever, rash and/or eosinophilia (>5%).	Discontinue study drug and notify Sponsor.

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

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

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

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

Laboratory Monitoring of Liver Function:

- Monitor liver enzymes, total bilirubin, total bile acids and INR at least 2 times a week until transaminase levels are <3x ULN, total bile acids are <5x ULN, total bilirubin <2x ULN and INR ≤1.5x ULN or levels stabilize, and the subject is asymptomatic.

- Obtain additional tests to evaluate liver function, such as fractionated bilirubin, as deemed appropriate.
- Thereafter, repeat testing will be performed as appropriate for the clinical circumstance until resolution or stability of transaminase values, total bilirubin, total bile acids and INR is achieved and any symptoms, if present, have abated.

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

6.1.3. QT Stopping Criteria

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

- QTcF >500 msec OR uncorrected QT >600 msec
- Change from Screening in QTcF of >60 msec

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

6.1.4. Suicidality Stopping Criteria

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

Individuals who answer “yes” to Question 3, 4, or 5 in the suicidal ideation section of the C-SSRS at screening or baseline are not eligible for this study. Any subject who exhibits any Suicidal Behavior or Suicidal Ideation (eg, answers “yes” to Question 3, 4, or 5 in the suicidal ideation section of the C-SSRS) will have study drug immediately discontinued and should be evaluated by a psychiatrist. This safety finding will be considered an AESI if it is not an SAE (eg, requiring hospitalization) (see Section 7.2.8).

6.1.5. Depression or Anxiety Stopping Criteria

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. This will be considered an AESI if it is not an SAE (eg, requiring hospitalization) (see Section 7.2.8).

6.1.6. Adrenal Insufficiency Stopping Criteria

Symptoms of adrenal insufficiency include weakness, tiredness, anorexia, nausea, vomiting, abdominal pain, orthostasis and muscle and joint aches. Weight loss and hypotension (eg, systolic blood pressure <110 mmHg) are also associated with adrenal insufficiency. Hyponatremia, hyperkalemia, hypercalcemia, azotemia, anemia, and eosinophilia may accompany adrenal insufficiency. It is important to note that many of these signs, symptoms and laboratory findings are nonspecific and commonly occur in persons without adrenal

insufficiency. The Investigator should use their clinical judgment when determining whether the signs, symptoms or laboratory findings are isolated AEs or are possibly due to adrenal insufficiency.

The Investigator is strongly encouraged to contact the medical monitor to review the presentation and discuss the plan for subjects with any AEs of adrenal insufficiency or cortisol measurements below the normal range.

If a subject develops clinical and/or laboratory findings of adrenal insufficiency that are confirmed with serum cortisol measurement, the AE of "adrenal insufficiency" should be reported on the AE/SAE CRF. The sign(s), symptom(s) and laboratory findings resulting in the diagnosis of adrenal insufficiency will be collected on separate Adrenal Insufficiency CRF and should not be individually recorded on the AE CRF. If the serum cortisol level is within the normal range, the individual symptoms and/or other laboratory findings should be reported as individual AEs.

In the absence of clinical or laboratory findings of adrenal insufficiency, unconfirmed serum cortisol levels below the normal range should not be reported as AE. Confirmed by repeat serum cortisol levels below the normal range, even in the absence of clinical or laboratory findings of adrenal insufficiency, are to be reported as an AE of adrenal insufficiency.

If at a telephone visit or at an unscheduled contact, the subject reports symptoms compatible with adrenal insufficiency, dosing with study drug should be suspended. The subject should report to the clinic the next morning at 8 A.M. for serum cortisol measurement. The sample should be sent to the clinic's local laboratory for an expedited measurement. A second sample should be sent to the central laboratory for centralized measurement. The Investigator should use the results from the local laboratory to determine if dosing may be resumed (normal serum cortisol measurement) or permanently discontinued.

If at a routinely scheduled clinic visit, the subject reports symptoms compatible with adrenal insufficiency, dosing with study drug should be suspended. A serum sample should be drawn and sent to the clinic's local laboratory for an expedited cortisol measurement. The Investigator should use the results from the local laboratory to determine if dosing may be resumed (normal serum cortisol measurement) or permanently discontinued. The serum cortisol measurement scheduled to be done by the central laboratory should be performed as scheduled.

If the serum cortisol level from a routinely scheduled clinic visit is below the normal range but the subject did not at the clinic visit report adverse events possibly related to adrenal insufficiency, the site should contact the subject, collect spontaneously reported AEs since the clinic visit and have the subject return to the clinic as soon as possible for a repeat 8 A.M. serum cortisol measurement done by the central laboratory. If the subject does not report symptoms of adrenal insufficiency and at the discretion of the Investigator, study drug may be continued until the serum cortisol measurement by the central laboratory is available. Alternatively, if the Investigator believes that the subject may have symptoms consistent with adrenal insufficiency, the study drug should be held and a serum sample sent to the clinic's local laboratory for an expedited cortisol measurement. If the repeat serum cortisol level is

below the normal range either done by the central or local laboratory, study drug should be permanently discontinued, and the Early Termination Visit be conducted.

If a subject develops an AE of adrenal insufficiency meeting the seriousness criteria as defined in Section 7.2.2 or the event is severe in nature and in addition to suspending administration of study medication, the Investigator may consider treatment with glucocorticoid therapy. The route, type and dose of glucocorticoid treatment as well as the duration of therapy are at the discretion of the Investigator and should be in accordance with the local treatment guidelines for the treatment of adrenal insufficiency.

If a subject develops an adrenal insufficiency AE meeting the seriousness criteria as defined in Section 7.2.2 or the event is severe in nature, regardless of the outcome of the serum cortisol measurement, study drug should be permanently discontinued, and the subject should undergo the Early Termination Visit.

All serious or non-serious AEs of adrenal insufficiency are considered AESI.

6.1.7. Reproductive Hormone Stopping Criteria

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

6.1.8. Platelet Stopping Criteria

- Platelet counts <75,000/µL (Grade 3) should be confirmed with repeat laboratory testing within 72 hours of receipt of the initial test results.
- Platelet counts <75,000/µL should be monitored every 48 to 72 hours; if they decrease below 50,000 mm^3, fail to normalize after 7 days, or clinical complications of thrombocytopenia develop, drug should be discontinued immediately, and the subject withdrawn from the study.
- Platelet counts <50,000/µL should retest as soon as possible and discontinue drug immediately with withdrawal of the subject if testing is confirmatory.

6.1.9. Study Stopping Criteria

If any of the following criteria are met, the study will be stopped.

1. If 3 or more subjects on active drug experience a drug-related AESI
2. If 1 or more subjects on active drug experience a drug-related TEAE that is serious (TESAE) and results in death (Grade 5)
3. Any other safety trend or finding that creates an unacceptable risk-benefit profile for subjects participating in the study

Intensity should be evaluated per definitions in Section 7.2.3.1. Seriousness criteria are provided in Section 7.2.2. An unblinded Medical Monitor separate from the study team will monitor if study stopping criteria are met.

6.1.10. Clinically Significant Adverse Events

Clinically significant AEs include but are not limited to SAEs, AEs leading to study drug discontinuation/study withdrawal (eg, based on stopping criteria in Section 6.1), DLTs (Section 6.1.1), and AESIs (Section 7.2.8).

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

6.2. Subject Withdrawal from the Study

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

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

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

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

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

If possible, an Early Termination Visit (see Schedule of Activities in Section 12.2) should be conducted before subject withdrawal. The Investigator must document the date and primary reason for the withdrawal on the appropriate eCRF. Subjects who withdraw prematurely may be replaced at the discretion of the Sponsor to ensure adequate numbers of evaluable subjects.

6.3. Lost to Follow-up

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

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

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

7. STUDY ASSESSMENTS AND PROCEDURES

The timing of study assessments and procedures is provided in the Schedule of Activities in Section 12.2.

7.1. Safety Assessments

Safety assessments will include monitoring and recording all AEs (including SAEs, AEs leading to discontinuation/withdrawal, DLTs, and AESIs), physical examination, vital signs assessment, ECGs, and clinical laboratories, including serum cortisol and monitoring for suicide risk using the C-SSRS. AE procedures are described in Section 7.2.

7.1.1. Physical Examination

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

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

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

7.1.2. Vital Signs

Vital signs consist of systolic and diastolic blood pressure, pulse rate, respiration rate, and body temperature. The subject should rest for at least 5 minutes before vital signs measurement without speaking or using a cellphone. The subject should be sitting in an upright position with feet flat on the floor and the measurement arm supported at heart level. Blood pressure should be taken in the same arm at each visit, if possible. Vital signs will be measured as specified in the Schedule of Activities (Section 12.2) and as clinically indicated.

7.1.3. Body Weight and Height

Total body weight (actual body weight) will be measured as specified in the Schedule of Activities (Section 12.2) using a calibrated balance. Height will be recorded at the Screening Visit only. BMI will be calculated using these measurements.

7.1.4. Electrocardiogram

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

Refer to Section 6.1.3 for QT individual treatment-stopping criteria and any additional ECGs that may be necessary.

7.1.5. Clinical Laboratories

Clinical laboratory assessments include hematology, clinical chemistry, including cortisol, HbA1c, coagulation, lipid panel, thyroid panel, urinalysis, and a hormone panel. eGFR for screening will be calculated from blood creatinine measured as part of Screening clinical chemistry. A complete list of study-required clinical laboratory tests is provided in Section 12.4.

Samples for clinical laboratories will be collected consistently at the beginning of each visit at approximately 8 A.M. See the Schedule of Activities (Section 12.2).

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

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

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

7.1.6. Psychiatric Evaluations

7.1.6.1. Columbia-Suicide Severity Rating Scale (C-SSRS)

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

Refer to Section 6.1.4 for suicidality individual treatment-stopping criteria.

7.2. Adverse Events and Serious Adverse Events

7.2.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject participating in a clinical trial. Examples of AEs include but are not limited to:

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

A TEAE is defined as an AE that occurs during or after administration of the first dose of study drug until 30 days after the final dose of study drug (Follow-up Visit). For AEs that occur on the date of the first dose of study drug, the time of onset (before or after intake of study drug) must be specified.

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

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

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

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

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

7.2.2. Definition of Serious Adverse Event

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

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

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

Hospitalization does not include rehabilitation, hospice, or skilled nursing facilities; respite care; nursing homes; or same-day surgeries (as outpatient/same day/ambulatory procedures).

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

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

7.2.3. Classification of an Adverse Event

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

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

7.2.3.1. Severity

The Investigator will assess the severity of each AE according to the National Cancer Institute CTCAE version 5.0 (CTCAE 2017), which is summarized in Table 3.

Table 3. Severity of Adverse Events

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

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

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. Severe is a category used for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met at least one of the criteria for an SAE listed in Section 7.2.2, such as resulting in hospitalization.

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

7.2.3.2. Relationship to Study Drug

The Investigator will assess the relationship of each AE to study drug according to the categories in Table 4. This assessment will serve to determine whether there exists a reasonable possibility that the study drug caused or contributed to the AE.

Table 4. Relatedness of Adverse Event to Study Drug

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

Abbreviation: AE, adverse event.

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

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

7.2.3.3. Action Taken

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

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

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

7.2.3.4. Outcome

The outcome of each AE will be recorded as one of the categories in Table 5.

Table 5. Outcome of Adverse Events

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

Abbreviation: AE, adverse event.

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

AEs will be recorded from the time the ICF is signed until the end of the follow-up period. AEs will be assessed at each study visit, and subjects should be encouraged to contact the study site to report AEs that occur between scheduled visits. AEs that occur in the time period between

informed consent and the first dose of study drug of the Treatment Period should be recorded but will not be considered TEAEs.

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

7.2.5. Adverse Event Reporting

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

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

7.2.6. Serious Adverse Event Reporting

Throughout the study, the Investigator is to report all SAEs, regardless of suspected causality, to the Sponsor within 24 hours of learning of its occurrence using the SAE Report Form. AESIs (see Section 7.2.8) will also be reported in the electronic data capture (EDC) system and on the SAE Report Form and must be clearly differentiated from SAEs. Completion guidelines are provided in the Investigator Site File. The Investigator must assess and record the relationship of each event to study drug. Any SAE experienced after the follow-up period should be reported to the Sponsor only if the Investigator suspects a causal relationship to the study drug.

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

The Sponsor will ensure that all suspected unexpected serious adverse reactions (SUSARs), determined based on the Reference Safety Information in the most recent version of the IB at the time of the event, will be reported to the FDA and to all Institutional Review Boards (IRBs)/Ethics Committees (ECs) overseeing the conduct of the study, in accordance with FDA 21 CFR 312.32.

7.2.7. Reporting of Pregnancy

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

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

Should a woman become pregnant while taking tildacerfont (in utero exposure), the pregnancy will be followed to assess fetal growth parameters, neonatal outcomes, and early child development outcomes through 3 years of age. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

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

7.2.8. Adverse Events of Special Interest

AESIs are those AEs (independent of seriousness criteria) that are of specific concern to this study and for which ongoing monitoring and communication with the Investigator and Sponsor may be appropriate. These events will be reported on the SAE Report Form, allowing for the collection of additional information, as warranted. The following may be considered AESIs for this study:

- Significant liver chemistry changes that do not satisfy study drug stopping rules (see Section 6.1.2). Cases of Hy's Law should also be reported as an AESI and an SAE.
- Suicidality as indicated by "yes" response to questions 3, 4, or 5 on the C-SSRS (see Section 6.1.4 regarding study drug stopping criteria for suicidality).
- Depression or anxiety that is moderate or severe (CTCAE Grade 2 or higher), as assessed by the Investigator (see Section 6.1.5 regarding study drug stopping criteria for depression or anxiety). This will be reported as an AESI and if seriousness criteria are met, reported as an SAE.
- Adrenal insufficiency

  Adverse events of adrenal insufficiency are considered AESIs (see Section 6.1.6). Both the AE/SAE CRF and Adrenal Insufficiency CRF should be completed. Symptoms of adrenal insufficiency will be reported as an SAE if they necessitate parental glucocorticoid administration by a health care professional and two of the following criteria are met: hypotensive (systolic blood pressure <100 mmHg); nausea or vomiting; severe fatigue; documented hyponatremia, hyperkalemia, or hypoglycemia.

  If hospitalization was required or the event of adrenal insufficiency is deemed to be an important medical event, life-threatening, results in a persistent or significant disability/incapacity or death, the adverse event should also be reported as an SAE.
  - For SAEs of adrenal insufficiency, records from the office of health care provider, emergency facility or hospital should be obtained as source documents to provide the

following information, in addition to completing the Adrenal Insufficiency CRF and the AE/SAE CRF:

- What type, dose and route of glucocorticoid was administered and the duration of administration?
- What concomitant medications were administered?
- What clinical laboratory results are available?
- What AEs occurred?
- What was deemed to be the inciting factor leading to adrenal crisis?

7.2.9. Safety Oversight

A Safety Review Committee (SRC) composed of at least two clinical and one biostatistical representatives will convene and review safety data on a regular basis. Ad hoc meetings will occur if drug-related AESIs or drug-related SAEs are observed to determine if there is an impact to study conduct.

7.3. Efficacy Assessments

The primary efficacy assessment is measurement of serum DHEAS levels.

Exploratory efficacy assessments will include assessment of various serum hormone levels: ACTH, DHEA, T, A4, 17-OHP, 11OHA4, 11OHT, 11KA4, 11KT, LH, FSH, SHBG, and estradiol.

7.4. Pharmacokinetic Assessments

PK samples will be collected at Day 1, and Weeks 4, 8, and 12 and will consist of a single timepoint draw at 8 A.M. (±1 hour).

8. STATISTICAL CONSIDERATIONS

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

8.1. Sample Size Determination

A sample size of 33 subjects with 2:1 randomization will provide at least 80% power to detect a difference of 164 mcg/dL in mean DHEAS between at least one dose of tildacerfont and placebo assuming a standard deviation of 154 mcg/dL and a two-sided alpha of 0.05. Accounting for a 15% drop out, the final sample size is N=39 (n=26 for tildacerfont group and n=13 for placebo).

Subjects will be randomized using the strata of screening DHEAS (≤1.2x ULN, >1.2x ULN).

8.2. Populations for Analyses

The Intent-to-Treat (ITT) Population will include all subjects randomized in the study.

The modified Intent-to-Treat (mITT) Population will include subjects in the ITT population who have at least one dose of study drug, a baseline DHEAS assessment and at least one post baseline DHEAS assessment.

The Safety Population will include all subjects who receive at least 1 dose of study drug in the study.

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

8.3. Statistical Analyses

8.3.1. General Considerations

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

All continuous data will be summarized using an 8-point descriptive summary (n, mean, standard deviation, median, interquartile range [25th percentile (Q1), 75th percentile (Q3)], minimum, and maximum), as available. Categorical data will be summarized using the frequency of events and percentage of total events.

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

8.3.2. Demographics and Baseline Characteristics

Listings and summary tables will be provided for demographics (age, sex, ethnicity, and race) and baseline characteristics (weight, height, and BMI) for the ITT Population.

Baseline clinical characteristics and history will be summarized for the ITT Population.

8.3.3. Concomitant Medications

Summary tables will be provided for concomitant medications. Prescription, OTC, and alternative medication use will be listed.

8.3.4. Efficacy Analyses

All efficacy analyses will be conducted on mITT Population using a 2-sided alpha of 0.05. No adjustment for multiplicity is planned.

The primary endpoint, the change from baseline in DHEAS, will be used to evaluate the preliminary efficacy of tildacerfont therapy relative to placebo and will be summarized using an analysis of covariance (ANCOVA) model with baseline DHEAS as a covariate and randomization strata and dose level as independent variables. Each Treatment Period's final DHEAS assessment (ie, Week 4, Week 8, and Week 12) is the dependent variable. Additional covariates may be added in the SAP.

The proportion of subjects meeting specific DHEAS thresholds will be summarized using exact tests through logistic regression using a similar variable structure as the primary endpoint:

- DHEAS ≥30% reduction from baseline vs <30% reduction from baseline
- DHEAS ≤ULN vs >ULN.

Additional covariates may be added in the SAP. Missing values for proportion endpoints will not be imputed and will be assumed to be failures.

Exploratory hormone and androgen endpoints will be summarized using an ANCOVA model using a similar variable structure as the primary endpoint. Additional endpoints may be specified in the SAP.

8.3.5. Safety Analyses

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

8.3.5.1. Extent of Exposure

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

8.3.5.2. Adverse Event Data

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

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

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

8.3.5.3. Clinical Laboratory Data

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

Laboratory data will be summarized in terms of observed values, changes from baseline, values relative to normal ranges, and changes from baseline relative to normal ranges.

8.3.5.4. Vital Signs Data

Vital signs data will be summarized within appropriately defined categories in terms of observed values (by time point), changes from baseline (by time point), and counts and percentages.

8.3.5.5. Electrocardiogram Data

The QTcF, PR interval, QT interval, QRS duration, and heart rate from standard digital 12-lead ECGs will be summarized within appropriately defined categories in terms of observed values, changes from baseline, and counts and percentages.

8.3.6. Pharmacokinetic Analyses

Concentration level at each visit will be summarized descriptively.

9. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1. Informed Consent

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

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

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

9.2. Study Discontinuation and Closure

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

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

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

9.3. Confidentiality and Privacy

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

All processing of personal data at the site and by the Sponsor must be carried out in accordance with any legislation concerning the protection of personal data. The Investigator must ensure

that the subject's privacy is maintained. The Sponsor will assign each subject a unique identifier. Any subject records or datasets that are transferred from the site to the Sponsor will contain this identifier only; subject names or any information that would make the subject identifiable will not be transferred.

9.4. Future Use of Stored Specimens and Data

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

9.5. Key Roles and Study Governance

9.5.1. Sponsor

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

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

9.5.2. Investigators

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

9.5.3. Institutional Review Board

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

9.6. Clinical Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative or designee will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, adherence to the protocol and to GCP, the progress of enrollment, and that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor

during these visits. See Section 10.4 for information on monitoring visits in the context of coronavirus disease 2019 (COVID-19).

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

Refer to Section 9.8.1 for information on eCRFs and source documents.

9.7. Quality Assurance and Quality Control

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

9.8. Data Handling and Record Keeping

9.8.1. Data Collection and Management Responsibilities

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

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

9.8.2. Study Records Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor or its designees, the Investigator agrees to keep records that include the identity of all subjects (sufficient

information to link records [eg, eCRFs and hospital records]), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and treatment disposition. The records should be retained by the Investigator for as long as ICH, local regulations, or the Clinical Study Agreement dictates, whichever is longer.

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

9.9. Protocol Deviations

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

If a protocol deviation is implemented to eliminate an immediate hazard before a protocol amendment can be submitted for IRB review and approval/favorable opinion (see Section 9.11), the deviation will be reported as soon as possible to 1) the IRB for review and approval/favorable opinion, 2) the Sponsor, and 3) regulatory authority(ies), if required by local regulations. Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to the Sponsor.

Protocol deviations will be included in the Clinical Study Report.

9.10. Publication and Data Sharing Policy

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

9.11. Amendments

The study shall be conducted as described in this protocol. All revisions to the protocol must be discussed with and prepared by the Sponsor. The Investigator should not implement any change to the protocol without a prior protocol amendment that has been reviewed by and received documented approval/favorable opinion from the IRB, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant protocol deviation must be documented (see Section 9.9).

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

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

10. COVID-19 RISK MITIGATION

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

Participation in a clinical study provides subjects with increased access to healthcare resources and reinforcement of appropriate practices during a time of increased infection risk. Study participants will have access to healthcare professionals on a more intensive schedule than in normal clinical practice for the management of PCOS. Each subject may have unique risk factors in the setting of possible COVID-19 infection and should discuss their individual risk-benefit assessment with their physician to determine if study participation is appropriate.

10.2. Study Conduct in the Context of COVID-19

If clinic visits are no longer possible because of COVID-19 restrictions, they will not be conducted. If lack of in-clinic assessments, including laboratory testing are not possible due to COVID-19, study drug may be discontinued if deemed necessary for safety. After a site reopens or a shelter-in-place order is lifted, attempts should be made to conduct any missed clinic visits.

If a subject or a member of the subject's household is suspected or confirmed to have COVID-19, the Investigator must consult with the Medical Monitor to determine the best course of action.

10.3. Subject Disposition in the Context of COVID-19

If a subject develops an active COVID-19 infection (whether confirmed or suspected) during the course of the study, the Investigator will work with the subject and the Medical Monitor to determine the best course of action, taking into consideration the AE and SAE guidelines in Section 7.2 and the individual stopping criteria for clinically significant AEs in Section 6.1.8. If study drug is discontinued or a subject is withdrawn from the study because of COVID-19, the reason for early termination will be captured in the EDC system as such.

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

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

11. REFERENCES

Carmina E, Rosato F, Jannì A. Increased DHEAs levels in PCO syndrome: evidence for the existence of two subgroups of patients. J Endocrinol Invest 1986; 9: 5–9.

Center for Disease Control and Prevention (CDC). PCOS (Polycystic Ovary Syndrome) and Diabetes. March 2020. https://www.cdc.gov/diabetes/basics/pcos.html

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. US Dept of Health and Human Services, National Institutes of Health, National Cancer Institute; 2017.

Mohammad MB, Seghinsara AM. Polycystic Ovary Syndrome (PCOS), Diagnostic Criteria and AMH. Asian Pac J Cancer Prev. 2017 Jan1;18 (1):17-21.

Rosenfield RL, Mortensen M, Wroblewski K, Littlejohn E, Ehrmann DA. Determination of the source of androgen excess in functionally atypical polycystic ovary syndrome by a short dexamethasone androgen-suppression test and a low-dose ACTH test. Human Reproduction. 2011; 26(11):3138-3146.

Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): The hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev. 2016;37:467-520.

Swart AC, Schloms L, Storbeck KH, et al. 11β-Hydroxyandrostenedione, the product of androstenedione metabolism in the adrenal, is metabolized in LNCaP cells by 5α-reductase yielding 11β-hydroxy-5α-androstanedione. J Steroid Biochem Mol Biol. 2013; 138: 132–142.

Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: Towards a rational approach. In: Polycystic Ovary Syndrome (Current Issues in Endocrinology and Metabolism), Dunaif A, Givens JR, Haseltine FP, Merriam GE (Eds), Blackwell Scientific Inc, Boston 1992. p.377.

12. APPENDICES

12.1. Optional DHEAS Screening Visit

CLINIC VISIT NUMBER	Optional Visit
STUDY DAY	≤60 days before Day 1
Informed Consent for DHEAS screening[1]	X
DHEAS [2]	X

Abbreviation: DHEAS, dehydroepiandrosterone sulfate

[1] Remote consenting is allowed.

[2] If documentation of prior DHEAS elevation is not present, the blood draw for the DHEAS sample will be obtained at 8 A.M. ± 1 hour.

12.2. Schedule of Activities

	Screening	Treatment Period 1			Treatment Period 2		Treatment Period 3		ETV/ Follow-up
CLINIC VISIT NUMBER		**1**		**2**		**3**		**4**	**5**
STUDY WEEK		**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
STUDY DAY	**≤30 days before Day 1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**Last dose +30 days**
Clinic Visit (C) [1], Telephone Contact (T) [1]	**C**	**C**	**T**	**C**	**T**	**C**	**T**	**C**	**C [2]**
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demography	X								
Medical history	X								
Prior medications from past year	X								
Concomitant medications	X	X	X	X	X	X	X	X	X

	Screening	Treatment Period 1			Treatment Period 2		Treatment Period 3		ETV/ Follow-up
CLINIC VISIT NUMBER		**1**		**2**		**3**		**4**	**5**
STUDY WEEK		**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
STUDY DAY	**≤30 days before Day 1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**Last dose +30 days**
Clinic Visit (C) [1], Telephone Contact (T) [1]	**C**	**C**	**T**	**C**	**T**	**C**	**T**	**C**	**C [2]**
Hepatitis B & C and HIV	X								
Urine drug screen	X								
Urinalysis	X	X [3]						X	
Pregnancy test [4]	X	X [3]		X		X		X	
PK [5]		X		X		X		X	
Vital signs, body weight, height [6]	X	X		X		X		X	
Full physical examination [7]		X [3]						X	
C-SSRS [8]	X	X		X		X		X	
Abbreviated physical examination [9]				X		X			
12-lead ECG	X	X [3]		X		X		X	
Hematology, clinical chemistry, coagulation, lipid panel, eGFR, thyroid panel, cortisol [10]	X	X		X		X		X	
DHEAS, progesterone, T, LH, FSH, SHBG, 17-OHP, prolactin [10]	X								
ACTH, DHEA, DHEAS, T, 17-OHP, A4, estradiol, LH, FSH, SHBG, 11OHA4, 11OHT, 11KA4, 11KT [10]		X		X		X		X	

	Screening	Treatment Period 1			Treatment Period 2		Treatment Period 3		ETV/ Follow-up
CLINIC VISIT NUMBER		**1**		**2**		**3**		**4**	**5**
STUDY WEEK		**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
STUDY DAY	**≤30 days before Day 1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**Last dose +30 days**
Clinic Visit (C) [1], Telephone Contact (T) [1]	**C**	**C**	**T**	**C**	**T**	**C**	**T**	**C**	**C [2]**
Randomization to treatment		X							
Dispense study drug [11]		X		X		X			
Dose escalation				X		X			
Study drug accountability				X		X		X	
Telephone contact to assess compliance and AEs			X		X		X		
Review AEs		X	X	X	X	X	X	X	X

Abbreviations: 11OHA4, 11β-hydroxyandrostenedione; 11OHT, 11β-hydroxytestosterone; 11KA4, 11-ketoandrostenedione; 11KT, 11-ketotestosterone; 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; AE, adverse event; C-SSRS, Columbia-Suicide Severity Rating Scale; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; ETV, Early Termination Visit; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; LH, luteinizing hormone; PK, pharmacokinetics; SHBG, sex hormone-binding globulin T, testosterone.

[1] All clinic visits and telephone contacts should be performed on the indicated study days. In cases where adherence to the foregoing schedule is not possible, the following visit windows apply: ±1 days for clinic visits and telephone contacts.
[2] All subjects will return to the clinic (or, at the discretion of the Investigator, be contacted via telephone) for the ETV/Follow-up Visit.
[3] Will be conducted pre-dose at Day 1
[4] A serum pregnancy test will be performed at screening. All other pregnancy tests will be urine pregnancy tests.
[5] Blood samples will be drawn for PK measurement at 8 A.M. (± 1 hour) on clinic visit days.
[6] Vital signs consist of systolic and diastolic blood pressure, pulse rate, respiration rate, and body temperature. Vital signs will be measured after a 5-minute rest period. Height is measured only at Screening Visit.
[7] A full physical examination may exclude rectal, genitourinary, and breast exams.
[8] See Section 7.1.6 for details on the administration of the C-SSRS.

[9] Abbreviated physical examinations at Visits 2 and 3 will be conducted directed by AEs.

[10] Blood draws for these laboratory assessment samples will be obtained at 8 A.M. (± 1 hour). On Day 1, blood draws should be performed prior to the first dose of study drug.

[11] Study drug will be taken daily with an evening meal (with approximately <50% fat content), which should be eaten between 6 P.M. and midnight. Study drug may be consumed up to 30 minutes after completing the evening meal, if necessary.

12.3. Appendix of Prohibited and Cautionary Concomitant Medications

Refer to Section 5.6.1 for more information on 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. This list is intended to show more commonly encountered drugs that subjects may be taking at Screening. Any drugs of concern should be discussed with the Medical Monitor.

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

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

12.4. Appendix of Clinical Laboratory Tests

Refer to Section 7.1.5 for more information on clinical laboratory tests.

Laboratory Assessments	Parameters
Hematology	Platelet count
	RBC count RBC indices: MCV, MCH, % reticulocytes
	Hemoglobin
	Hemoglobin A1c
	Hematocrit
	WBC count Differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils
Clinical Chemistry	Potassium Calcium Sodium BUN Creatinine Total protein Fasting glucose ALP ALT/SGPT AST/SGOT GGT Total and direct bilirubin Total bile acids Fasting insulin
Coagulation	PT/INR, PTT
Lipid Panel	Total cholesterol, LDL, HDL, triglycerides
Thyroid Panel	T3 (free and total), T4 (free and total), TSH
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, by dipstick Microscopic examination (if blood or protein is abnormal) Urine pregnancy testing
Hormones	DHEAS, ACTH, DHEA, T, A4, 17-OHP, 11OHA4, 11OHT, 11KA4, 11KT, FSH, LH, SHBG, prolactin, cortisol, estradiol, progesterone (blood [screening only]), HCG (pregnancy test at screening only)

Abbreviations: 11KA4, 11-ketoandrostenedione; 11KT, 11-ketotestosterone; 11OHA4, 11β-hydroxyandrostenedione; 11OHT, 11β-hydroxytestosterone; 17-OHP,17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone, corticotropin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl transferase; HCG, human chorionic gonadotropin; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; LH, luteinizing hormone; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; SHBG, sex hormone-binding globulin; T, testosterone; TSH, thyroid-stimulating hormone; WBC, white blood cell.