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A 3-Month Phase 2 Study to Evaluate the Safety and Efficacy of SPR001 in Subjects with Classic Congenital Adrenal Hyperplasia

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Investigational Medicinal Product:	SPR001
Indication:	Classic congenital adrenal hyperplasia (CAH)
Sponsor:	Spruce Biosciences, Inc. 1700 Montgomery St, Suite 212 San Francisco, CA 94111
Principal Investigator:	Deborah Merke, MD, MS
Registry:	ClinicalTrials.gov

INVESTIGATOR PROTOCOL AGREEMENT PAGE

A 3-Month Phase 2 Study to Evaluate the Safety and Efficacy of SPR001 in Subjects with Classic Congenital Adrenal Hyperplasia

Study Number: SPR001-202
Protocol Version: 1.1
Protocol Date: 20 Dec 2018

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

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

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

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

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

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

Site Name: National Institutes of Health

Principal Investigator Name: Deborah P. Merke, M.D., M.S.

_____ _____

Investigator's Signature **Date**

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LIST OF ABBREVIATIONS

11oxC19	11-oxygenated 19-carbon (steroids)
17-OHP	17-hydroxyprogesterone
ACTH	adrenocorticotropin hormone, corticotropin
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BDI-II	Beck Depression Inventory-II
BID	twice a day
BMI	body mass index
BUN	blood urea nitrogen
BW	body weight
C-SSRS	Columbia-Suicide Severity Rating Scale
CAH	congenital adrenal hyperplasia
C_{max}	maximum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	corticotropin-releasing factor

CRF_1	corticotropin-releasing factor type-1
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HADS	Hospital Anxiety and Depression Scale
HbA1c	hemoglobin A1c
HDPE	high-density polyethylene
HEENT	head, eyes, ears, neck, and throat
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment (of acne severity)
INR	international normalized ratio

IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
LFT	liver function test
LH	luteinizing hormone
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mFG	modified Ferriman Gallwey (score for hirsutism)
M.I.N.I.	Mini International Neuropsychiatric Interview
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
OTC	over the counter
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
QD	once a day
QoL	quality of life
QTcF	Fridericia-corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SF-36	Short Form 36

SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SHBG	sex hormone–binding globulin
SRC	safety review committee
TART	testicular adrenal rest tumor
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WOCP	woman/women of childbearing potential

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Study Number: SPR001-202

Study Title

A 3-Month Phase 2 Study to Evaluate the Safety and Efficacy of SPR001 in Subjects with Classic Congenital Adrenal Hyperplasia

Study Rationale

Congenital adrenal hyperplasia (CAH) is a chronically debilitating genetic disorder caused by a critical enzymatic deficiency in the steroidogenic pathways that synthesize the corticosteroids aldosterone and cortisol within the adrenal gland. The hallmark of CAH is cortisol deficiency, which disrupts the balance of the hypothalamic-pituitary-adrenal (HPA) axis by removing the negative feedback to the hypothalamus provided by normal levels of cortisol. This leads to the overproduction of corticotropin-releasing factor (CRF) by the hypothalamus, consequent overproduction of adrenocorticotropin hormone (ACTH) by the pituitary gland, and consequent adrenal hyperplasia and overproduction of cortisol precursors such as 17-hydroxyprogesterone (17-OHP) by the adrenal gland, leading to androgen overproduction. Androgen excess may result in precocious puberty; seborrhea; impaired fertility; irregular menses, amenorrhea, acne, hirsutism, and virilization in females; and testicular adrenal rest tumors (TARTs) in males. Additionally, patients with the salt-wasting form of CAH have severe aldosterone deficiency, which leads to sodium depletion, potassium elevation, decreased blood volume, dehydration, and hypotension that can be life threatening in early infancy. Current treatment for CAH centers around using chronic high-dose glucocorticoids to replace cortisol, a problematic therapy with significant side effects, a narrow therapeutic window, and overall poor treatment effectiveness. Given the serious nature of CAH and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with CAH.

SPR001, a high-affinity and selective small-molecule antagonist of CRF type 1 (CRF_1) receptors in the pituitary gland, is being studied for the treatment of CAH on the basis of its ability to reduce the hypothalamic drive of CRF on the pituitary, thereby reducing ACTH overproduction by the pituitary and consequently reducing the overproduction of 17-OHP and androgens by the adrenal glands. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced reductions in ACTH and 17-OHP in subjects with CAH (Turcu et al, 2016). SPR001 has been shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies, 2 completed Phase 1 clinical studies in healthy volunteers, and an ongoing Phase 2 clinical study in which subjects with CAH are treated for 2 weeks with any particular dose level of study drug (Study SPR001-201). Given that patients with CAH may require long-term treatment with SPR001, this study will investigate the extended use of SPR001 over

a 3-month period in combination with replacement glucocorticoids and mineralocorticoids in the treatment of CAH.	
Objectives	**Endpoints**
Primary	
• To evaluate the safety of SPR001 in subjects with CAH	• Adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation/withdrawal, dose-limiting toxicities (DLTs), and AEs of special interest (AESIs) • Physical examination findings • Vital signs • Changes in electrocardiogram (ECG) • Changes in clinical laboratory values • Changes in the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Hospital Anxiety and Depression Scale (HADS)
Secondary	
• To evaluate the efficacy of SPR001 in subjects with CAH in terms of changes in hormones	• Changes in ACTH, 17-OHP, androstenedione, and testosterone
Exploratory	
• To evaluate the effect of SPR001 on quality of life (QoL), metabolic parameters, exploratory adrenal hormones, and sex-specific outcomes in subjects with CAH	• Changes in QoL as measured using the Short Form 36 (SF-36), Patient Global Impression of Change (PGIC), bother score, and CAH signs and symptoms interview • Changes in fasting glucose, hemoglobin A1c (HbA1c), fasting insulin, and lipid profile • Changes in body weight (BW) and body mass index (BMI) • Changes in exploratory adrenal hormones • Changes in TARTs and on semen analysis in male subjects • Changes in acne, hirsutism, and menstrual cyclicity in female subjects
Study Design This is a Phase 2 study of SPR001 for the treatment of classic CAH that will provide 12 weeks of open-label treatment to eligible subjects. To be eligible for this study, an individual must	

either have completed Study SPR001-201 or meet criteria for SPR001-naïve subjects outlined under Eligibility Criteria.

Initial subjects who enroll in this study will be treated with SPR001 at 400 mg once a day (QD) during the treatment period. For subjects who enroll later on in this study, the dose strength may be increased or decreased (by no more than 2-fold) and/or the dose regimen may be adjusted (e.g., to twice-daily [BID] dosing, a regimen being tested in Study SPR001-201). In general, subjects are expected to complete the study at the dose strength and on the dose regimen at which they started the study, unless they experience a clinically significant AE that would warrant a dose reduction.

A safety review committee (SRC) will review the available safety, pharmacokinetics (PK), and pharmacodynamics (PD) data from Study SPR001-201 Cohorts B/C/D and from this study on an ongoing basis and provide recommendations to the Sponsor, who will ultimately decide on any dosing adjustments in this study.

The Schedule of Activities is provided in Section 1.3. Study visits will occur every 2 weeks during the treatment period and should be scheduled for the morning, to accommodate 8am laboratory assessments. Study visits for screening and at Day 1 (baseline), Week 4, Week 8, and Week 12 (end of treatment) will be conducted as outpatient clinic visits. Study visits at Week 2, Week 6, and Week 10 may be conducted as either outpatient clinic visits or in-home visits by qualified study personnel. A final safety follow-up outpatient clinic visit will occur 30 days after the last dose of study drug.

To reduce subject burden, the final safety follow-up visit in Study SPR001-201 for subjects completing that study and rolling over into this study may coincide with the screening visit of this study (with any overlapping assessments conducted only once). Subjects who completed the final follow-up visit in Study SPR001-201 >3 months before screening in this study and subjects naïve to SPR001 must complete anew all specified screening assessments for this study. Subjects will maintain a stable dose and regimen of glucocorticoids throughout this study.

Study Population

This study will enroll up to approximately 24 eligible subjects with classic CAH who either previously completed Study SPR001-201 or meet criteria for SPR001-naïve subjects outlined under Eligibility Criteria. The study will be conducted at approximately 8 investigative sites in the United States.

Eligibility Criteria

For Subjects Who Completed Study SPR001-201

Inclusion Criteria for Subjects Who Completed Study SPR001-201

- Is approved by the Sponsor's Medical Monitor
- Is on a stable regimen of glucocorticoid replacement for ≥12 weeks before baseline that is expected to remain stable throughout the study

- If screening for this study occurs >3 months after the subject's final follow-up visit in Study SPR001-201, the subject will have serum 17-OHP measured at screening. On the day of screening, the subject should take any morning glucocorticoid medication after the screening blood draw to allow for an unimpeded assessment of 17-OHP. The subject will be included if screening shows 17-OHP ≥800 ng/dL.
- Agrees to follow contraception guidelines (Section 5.3.5). Male subjects must also agree to refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug.
- Is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

Exclusion Criteria for Subjects Who Completed Study SPR001-201

- Experienced a clinically significant AE (defined in Section 7.2.7) considered at least possibly related to SPR001 in Study SPR001-201
- If screening for this study occurs >3 months after the subject's final follow-up visit in Study SPR001-201, the subject will be screened for any clinically significant unstable medical condition, medically significant illness, or chronic disease occurring within 30 days of screening, including but not limited to the following:
  - A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
  - Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2
  - Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
  - Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
- If screening for this study occurs >3 months after the subject's final follow-up visit in Study SPR001-201, the subject will be screened for clinically significant psychiatric disorders by history and from the Mini International Neuropsychiatric Interview (M.I.N.I.) conducted at screening. The subject will be excluded if screening reveals evidence of current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months.
- Is at increased risk of suicide on the basis of the Investigator's judgment or the results of the C-SSRS conducted at screening and baseline (e.g., C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)
- Has a HADS score >12 for either depression or anxiety at screening or baseline
- Clinically significant abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:

  - Clinically meaningful abnormal ECG results, in the opinion of the Investigator
  - Fridericia-corrected QT interval (QTcF) >450 msec for male participants or >470 msec for female participants
  - Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
  - Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- Subjects who routinely work overnight shifts require Medical Monitor approval for enrollment
- Females who are pregnant or lactating
- Use of any other investigational drug within 30 days or 5 half-lives (whichever is longer) before screening
- Use of prohibited concomitant medications (see Section 6.5.2.1), including rosiglitazone, testosterone, and strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids and birth control) within 30 days or 5 half-lives (whichever is longer) of baseline. Medications metabolized by CYP3A4, 2C8, 2C9, or 2C19, especially those that are sensitive substrates or substrates with narrow therapeutic ranges (see Section 6.5.2.2), should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before baseline.
- Donation of blood within 60 days before baseline or donation of platelets, white blood cells, or plasma within 15 days before baseline

<u>For SPR001-Naïve Subjects</u>

This study will offer enrollment to SPR001-naïve subjects with eligibility criteria similar to those of Study SPR001-201 but will also seek to include an enriched population of subjects with CAH who exhibit clinically significant sequelae of androgen excess, specifically males 18 to 35 years old with TARTs and adult females with clinically significant acne, hirsutism, and/or ovulatory dysfunction. This study will initially allow enrollment of at least 3 subjects who meet general eligibility criteria for all SPR001-naïve subjects and who may or may not meet additional inclusion criteria for an enriched population of SPR001-naïve subjects. At any time thereafter, the Sponsor may decide to require all SPR001-naïve subjects who enroll subsequently to satisfy the additional inclusion criteria for an enriched population of SPR001-naïve subjects.

Inclusion Criteria for All SPR001-Naïve Subjects

- Male and female subjects ≥18 years old
- Has a documented historical diagnosis of classic CAH due to 21-hydroxylase deficiency based on documented genetic mutation or elevated 17-OHP
- Known or suspected differential diagnosis of any of the other known forms of CAH, including non-classic CAH, requires Medical Monitor approval for enrollment

- Has serum 17-OHP ≥800 ng/dL at screening. On the day of screening, the subject should take any morning glucocorticoid medication after the screening blood draw to allow for an unimpeded assessment of 17-OHP.
- Is on a stable regimen of glucocorticoid replacement for ≥12 weeks before baseline that is expected to remain stable throughout the study
- Agrees to follow contraception guidelines (Section 5.3.5). Male subjects must also agree to refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug.
- 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

Additional Inclusion Criteria for Enriched Population of SPR001-Naïve Subjects

- If male, must be 18 to 35 years old, inclusive.
- If male, must have a diagnosis of TART(s) confirmed via scrotal ultrasound at screening with at least 1 lesion having a diameter ≥4 mm
- If female, must have at least one of the following clinically significant sequelae of androgen excess:
  - Clinically significant acne defined as an Investigator's Global Assessment (IGA) score ≥2 at screening
  - Clinically significant hirsutism defined as a modified Ferriman-Gallwey (mFG) score ≥6 at screening
  - Verifiable history (based on medical records or ability to obtain an accurate history from the individual) of ovulatory dysfunction defined as having at least 1 year of menstrual cycles that last ≥45 days or having ≤8 menstrual periods within the past year, if the subject is not on a hormonal contraceptive

Exclusion Criteria for All SPR001-Naïve Subjects

- Has had a clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
  - A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
  - Presence of clinically significant renal disease, as evidenced by an eGFR of <60 mL/min/1.73 m^2
  - Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
  - Confirmed positive test at screening for active hepatitis B, hepatitis C, or HIV
- Had or has a clinically significant psychiatric disorder either by history or from the M.I.N.I. conducted at screening. The subject will be excluded if screening reveals evidence of current major depressive episode, bipolar disorder, schizophrenia, schizoaffective

disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months.

- Is at increased risk of suicide on the basis of the Investigator's judgment or the results of the C-SSRS conducted at screening and baseline (e.g., C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)
- Has a HADS score >12 for either depression or anxiety at screening or baseline
- Clinically significant abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:
  - Clinically meaningful abnormal ECG results, in the opinion of the Investigator
  - QTcF >450 msec for male participants or >470 msec for female participants
  - ALT >2x ULN
  - Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- Has a history that includes bilateral adrenalectomy or hypopituitarism
- Subjects who routinely work overnight shifts require Medical Monitor approval for enrollment
- Females who are pregnant or nursing
- Use of any other investigational drug within 30 days or 5 half-lives (whichever is longer) before screening
- Use of prohibited concomitant medications (see Section 6.5.2.1), including rosiglitazone, testosterone, and strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids and birth control) within 30 days or 5 half-lives (whichever is longer) of baseline. Medications metabolized by CYP3A4, 2C8, 2C9, or 2C19, especially those that are sensitive substrates or substrates with narrow therapeutic ranges (see Section 6.5.2.2), should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before baseline.
- Donation of blood within 60 days before baseline or donation of platelets, white blood cells, or plasma within 15 days before baseline

Investigational Drug

The drug product SPR001 is a small-molecule CRF_1 receptor antagonist and will be supplied as white, hard-gelatin capsules containing either 50 mg or 200 mg of drug substance with no excipients.

Dose, Route, Regimen

Initial subjects who enroll in this study will be treated with oral study drug at 400 mg QD at 10pm for 12 weeks. This dose is within the range of doses that were well tolerated and reduced key hormones (ACTH, 17-OHP, and androstenedione) in subjects with CAH in Cohort A of Study SPR001-201. For subjects who enroll later on in this study, the dose strength may be increased or decreased (by no more than 2-fold) and/or the dose regimen may be adjusted (e.g., to BID dosing, a regimen being tested in Study SPR001-201). In general, subjects are expected to complete the study at the dose strength and on the dose regimen at which they started the study, unless they experience a clinically significant AE that would warrant a dose reduction. An SRC will review the available safety, PK, and PD data from Study SPR001-201 Cohorts B/C/D and from this study on an ongoing basis and provide recommendations to the Sponsor, who will ultimately decide on any dosing adjustments in this study.

Study drug will be taken with a meal or 5 to 15 minutes after consumption of a standardized snack. On the mornings of all study visits, including the screening visit, subjects should hold off on taking any morning glucocorticoid medication (and on taking study drug, if a morning dose is added and if applicable to the visit) until after laboratory assessments are completed. On all other days during the study, subjects should take any morning glucocorticoid medication (and morning dose of study drug, if applicable) at their usual time.

If a subject experiences a DLT (defined as a Grade 3 or higher treatment-emergent adverse event [TEAE] considered at least possibly related to study drug), the Investigator may reduce the subject's daily dose of SPR001 (by 50 to 200 mg), depending on the TEAE and upon discussion with the Sponsor's Medical Monitor. Study drug will be discontinued in subjects who experience clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria (Section 7.2).

Study Duration

The expected duration of study participation for each subject is up to approximately 7 months. This includes a screening period of 12 weeks, a treatment period of 12 weeks, and a safety follow-up period of 30 days.

Statistical Analyses

Sample Size

The total sample size of up to approximately 24 subjects in this study is based on an estimate of the number of subjects who may enroll either after completing Study SPR001-201 or as SPR001-naïve subjects. There is no statistical basis for the total sample size.

General Approach

Changes in primary, secondary, and exploratory endpoints will be analyzed over time, with change from baseline summarized for each post-baseline time point measured. If SPR001 dosing is adjusted for subjects who enroll later on in this study, data will be presented by SPR001 dose.

Demographics and Background

Demographics and subject background information such as disease characteristics will be summarized using descriptive statistics, including the number of subjects (n), mean, standard deviation, median, and range for continuous variables and count and percentage for categorical variables.

Safety Analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20 or higher and presented by System Organ Class and Preferred Term. TEAEs will be listed by subject and summarized overall and by SPR001 dose, if applicable. The incidence of each TEAE will be tabulated and presented by maximum severity. The frequency (number and percentage) of subjects who experience ≥1 TEAE will be summarized. TEAEs potentially related to study drug, SAEs, AEs leading to study drug discontinuation/study withdrawal, DLTs, and AESIs will be summarized by frequency of subjects who experience ≥1 event and/or tabulated by incidence for each event.

Physical examination findings will be listed. Vital signs, ECG parameters, and clinical laboratory values will be listed and summarized using descriptive statistics. Investigators' assessments of ECG results will be listed and summarized in a frequency table. Clinical laboratory values may be presented in shift tables. Prior and concomitant medications will be listed. C-SSRS data will be listed. Data for the HADS (including anxiety and depression subscales) will be summarized using descriptive statistics.

An SRC will review safety data at regular intervals throughout the study (see Section 10.6).

Efficacy Analyses

Changes over time in hormones (ACTH, 17-OHP, androstenedione, testosterone, and exploratory adrenal hormones) will be summarized using descriptive statistics and presented in tables and/or graphs. Parametric (paired t test) or nonparametric (Wilcoxon signed rank) tests will be used to test the change from baseline depending on the data distribution.

Data for the SF-36 (including individual domain scores and summary scores) will be summarized using descriptive statistics. Data for the PGIC, the bother score, and the CAH signs and symptoms interview will be summarized using counts and percentages. Shifts in status from baseline to each post-baseline visit will be presented.

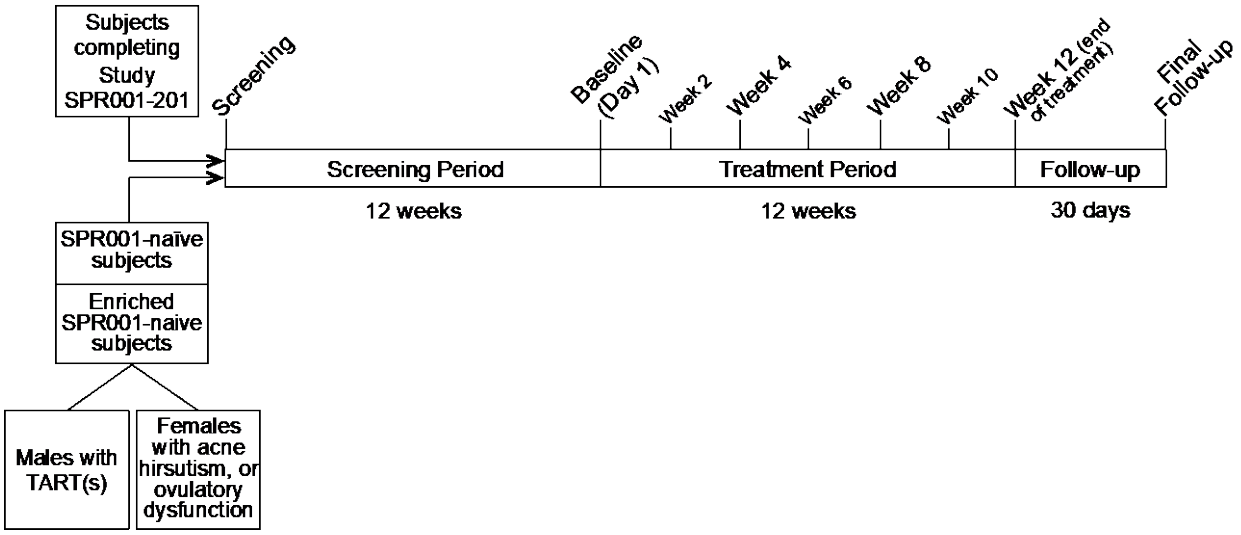
Changes over time in metabolic parameters (including fasting glucose, HbA1c, fasting insulin, lipid profile, BW, and BMI) will be summarized using descriptive statistics.

Changes over time in measures of TARTs and on semen analysis in male subjects and in measures of acne, hirsutism, and menstrual cyclicity in female subjects will be summarized using descriptive statistics.

Pharmacokinetic Analyses

PK may be assessed using a population PK approach.

1.2 Schema


Subjects completing Study SPR001-201
Screening
Baseline (Day 1)
Week 2
Week 4
Week 6
Week 8
Week 10
Week 12 (end of treatment)
Final Follow-up
Screening Period
Treatment Period
Follow-up
12 weeks
12 weeks
30 days
SPR001-naïve subjects
Enriched SPR001-naive subjects
Males with TART(s)
Females with acne hirsutism, or ovulatory dysfunction

1.3 Schedule of Activities

	Screening Period	Treatment Period							Follow-up/ET
VISIT NUMBER	**1[1] Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
STUDY WEEK		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
STUDY DAY[2]	**12 weeks before Day 1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**Last dose +30 days**
Site Visits[3]	**X**	**X**		**X**		**X**		**X**	**X**
Home Visits[4]			**X**		**X**		**X**		
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demography[5]	X								
Medical history[6]	X								
Prior medications[6]	X								
Concomitant medications[7]	X	X	X	X	X	X	X	X	X

[1] For subjects rolling over from Study SPR001-201, the final safety follow-up visit of Study SPR001-201 may coincide with the screening visit of this study (with any overlapping assessments conducted only once). If a subject completed the final follow-up visit of Study SPR001-201 ≤3 months before the screening period of this study, overlapping assessments conducted at that final follow-up visit need not be repeated at screening for this study. If a subject completed the final follow-up visit of Study SPR001-201 >3 months before the screening period of this study, all screening assessments must be conducted anew, including some additional screening assessments specified for such subjects.
[2] All visits should be performed on the indicated study days. In cases where this is not possible, the following visit windows apply: ±3 days for Visits 3 to 8 and ±7 days for the safety follow-up visit (Visit 9). All visits, including the early termination visit, should be scheduled for the morning, to accommodate 8am laboratory assessments.
[3] Study visits for screening; at Weeks 0, 4, 8, and 12; and at final follow-up must be conducted as in-clinic outpatient visits.
[4] Study visits at Weeks 2, 6, and 10 may be conducted as either in-clinic outpatient visits or in-home visits by qualified study personnel.
[5] Demographic information needs to be collected only for SPR001-naïve subjects.
[6] Full medical history and prior medications from the past year will be collected for SPR001-naïve subjects. If a subject completed the final follow-up visit in Study SPR001-201 before the screening period for this study, any significant medical history and medications taken during the intervening period should be captured.
[7] Subjects should be on a stable regimen of glucocorticoid replacement for a minimum of 12 weeks before baseline and throughout the treatment period. On the mornings of all study visits, including screening, subjects should hold off on taking any morning glucocorticoid medication until after laboratory assessments have been completed. On all other days during the study, subjects may take any morning dose of glucocorticoid medication at their usual time.

	Screening Period	Treatment Period							Follow-up/ET
VISIT NUMBER	**1[1] Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
STUDY WEEK		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
STUDY DAY[2]	**12 weeks before Day 1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**Last dose +30 days**
Site Visits[3]	**X**	**X**		**X**		**X**		**X**	**X**
Home Visits[4]			**X**		**X**		**X**		
Clinical laboratory[8,9]	X	X	X	X	X	X	X	X	X
HbA1c and fasting insulin[8]		X		X		X		X	
Key hormones[8,10]	X	X	X	X	X	X	X	X	X
Exploratory adrenal hormones[8,11]		X		X		X		X	
PK[8,12]	X	X		X		X		X	X
Hepatitis B & C and HIV screening[13]	X								
eGFR for screening[13,14]	X								
Pregnancy test for WOCP[15]	X	X		X		X		X	X
Vital signs[16] and body weight	X	X	X	X	X	X	X	X	X
Physical examination[17]	X	X		X		X		X	X

[8] Samples for these lab assessments will be obtained at the beginning of each study visit (8am), after overnight fast (nothing to eat since the previous midnight), and before the subject has taken any morning dose of glucocorticoid medication. If a morning dose of study drug is added, samples for these lab assessments will be obtained before the morning dose of study drug for that day (where applicable).
[9] Clinical laboratory assessments include hematology, clinical chemistry, fasting glucose, lipid panel, thyroid panel, urinalysis, LH, FSH, inhibin B, SHBG, renin, aldosterone, and, for females only, estradiol, prolactin, and progesterone.
[10] ACTH, 17-OHP, androstenedione, testosterone, and background glucocorticoid levels (cortisol/prednisolone/dexamethasone, depending on what the subject is taking) will be measured from blood samples. 17-OHP will also be measured from a saliva sample.
[11] A single blood sample will be drawn for measurement of exploratory adrenal hormones at each specified visit.
[12] A single blood sample will be drawn for PK measurement at each specified visit. The PK blood sample does not need to be obtained from SPR001-naïve subjects at screening.
[13] These screening assessments will be performed for SPR001-naïve subjects and for subjects who completed the final follow-up visit in Study SPR001-201 >3 months before the screening visit for this study.
[14] eGFR for screening will be calculated from blood creatinine measured as part of clinical chemistry during screening.
[15] A serum pregnancy test will be performed at screening for WOCP who are SPR001-naïve and for WOCP who completed the final follow-up visit in Study SPR001-201 >3 months before the screening visit for this study. All other pregnancy tests will be urine pregnancy tests.
[16] Systolic and diastolic blood pressure, pulse rate, body temperature, and respiration rate.
[17] A full physical examination will be conducted at baseline (Day 1) and end of treatment (Week 12) for all subjects. A full physical examination will also be conducted at screening for SPR001-naïve subjects and subjects who completed the final follow-up visit in Study SPR001-201 >3 months before the screening visit for this study. The full

	Screening Period	Treatment Period							Follow-up/ET
VISIT NUMBER	**1[1] Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
STUDY WEEK		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
STUDY DAY[2]	**12 weeks before Day 1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**Last dose +30 days**
Site Visits[3]	**X**	**X**		**X**		**X**		**X**	**X**
Home Visits[4]			**X**		**X**		**X**		
Scrotal ultrasound for males[18]	X	X						X	
Optional semen sample for males[19]		X						X	
Menstrual diary for females[20]	X	X	X	X	X	X	X	X	
12-lead ECG	X	X		X		X		X	
MINI Version 7.0.2[13]	X								
C-SSRS	X	X		X		X		X	
HADS	X	X		X		X		X	X
SF-36[21]		X		X		X		X	X
PGIC				X		X		X	X
Bother score		X		X		X		X	
CAH signs and symptoms interview		X		X		X		X	X
Dispense study drug[22]		X		X		X			

physical examination may exclude rectal, genitourinary, and breast exams. An abbreviated physical examination will be conducted at Weeks 4 and 8 and final follow-up. Height needs to be collected at screening only. As part of the examination of the skin, acne will be evaluated for all subjects using an IGA score at baseline and Weeks 4, 8, and 12; hirsutism will be evaluated for female subjects using an mFG score at baseline and Week 12. Female subjects will be asked about their last menstrual period as part of both full and abbreviated physical exams.

[18] For SPR001-naïve male subjects, a scrotal ultrasound will be conducted at the initial screening visit. For SPR001-experienced male subjects rolling over from Study SPR001-201, a scrotal ultrasound will be conducted at the initial screening visit only if the subject has not had a prior scrotal ultrasound within 3 months before screening. For all male subjects, if the prior or screening scrotal ultrasound reveals no evidence of TART, the scrotal ultrasound need not be repeated at either Day 1 or Week 12. If the prior or screening scrotal ultrasound does show evidence of TART(s), the scrotal ultrasound will be repeated at Day 1 and Week 12.

[19] All male subjects should be encouraged (though not required) to provide a semen sample. Semen will be collected from male subjects for analysis of sperm count, morphology, and motility.

[20] Female subjects will record menstrual information (including start and stop dates of menses and whether the flow was light, moderate, or heavy) in a menstrual diary throughout the 12-week screening period and the 12-week treatment period. A menstrual diary will be handed out at the screening visit and collected at the Day 1 visit, and a second menstrual diary will be handed out at the Day 1 visit and collected at the Week 12 visit.

[21] The 4-week SF-36 will be administered.

[22] Subjects will be dispensed a 4-week supply of study drug each time. If a morning dose of study drug is added, subjects should hold off on taking their morning dose of study drug on the mornings of all study visits until after laboratory assessments have been completed. On all other days during the study, subjects should take their morning dose of study drug (if applicable) at the usual time.

	Screening Period	Treatment Period							Follow-up/ET
VISIT NUMBER	**1[1] Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
STUDY WEEK		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
STUDY DAY[2]	**12 weeks before Day 1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**Last dose +30 days**
Site Visits[3]	**X**	**X**		**X**		**X**		**X**	**X**
Home Visits[4]			**X**		**X**		**X**		
Study drug accountability			X	X	X	X	X	X	
Review adverse events		X	X	X	X	X	X	X	X

Abbreviations: 17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropin hormone; CAH, congenital adrenal hyperplasia; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ET, early termination; FSH, follicle-stimulating hormone; HADS, Hospital Anxiety and Depression Scale; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment (score for acne); LH, luteinizing hormone; M.I.N.I., Mini International Neuropsychiatric Interview; mFG, modified Ferriman-Gallwey (score for hirsutism); PD, pharmacodynamics; PGIC, Patient Global Impression of Change; PK, pharmacokinetics; SF-36, Short Form 36; SHBG, sex hormone–binding globulin; WOCP, women of childbearing potential.

2 INTRODUCTION

2.1 Study Rationale

CAH is a chronically debilitating genetic disorder caused by a critical enzymatic deficiency in the steroidogenic pathways that synthesize the corticosteroids aldosterone and cortisol within the adrenal gland. The hallmark of CAH is cortisol deficiency, which disrupts the balance of the HPA axis by removing the negative feedback to the hypothalamus provided by normal levels of cortisol. This leads to the overproduction of CRF by the hypothalamus, consequent overproduction of ACTH by the pituitary gland, and consequent adrenal hyperplasia and overproduction of cortisol precursors such as 17-OHP by the adrenal gland, leading to androgen overproduction. Androgen excess may result in precocious puberty; seborrhea; impaired fertility; irregular menses, amenorrhea, acne, hirsutism, and virilization in females; and TARTs in males. Additionally, patients with the salt-wasting form of CAH have severe aldosterone deficiency, which leads to sodium depletion, potassium elevation, decreased blood volume, dehydration, and hypotension that can be life threatening in early infancy. Current treatment for CAH centers around using chronic high-dose glucocorticoids to replace cortisol, a problematic therapy with significant side effects, a narrow therapeutic window, and overall poor treatment effectiveness. Given the serious nature of CAH and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with CAH.

SPR001, a high-affinity and selective small-molecule antagonist of CRF_1 receptors on the pituitary gland, is being studied for the treatment of CAH on the basis of its ability to reduce the hypothalamic drive of CRF on the pituitary, thereby reducing ACTH overproduction by the pituitary and consequently reducing the overproduction of 17-OHP and androgens by the adrenal glands. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced reductions in ACTH and 17-OHP in subjects with CAH (Turcu et al, 2016). SPR001 has been shown to have an acceptable safety and tolerability profile in nonclinical toxicology studies, 2 completed Phase 1 clinical studies in healthy volunteers, and an ongoing Phase 2 clinical study in which subjects with CAH are treated for 2 weeks with any particular dose level of study drug (Study SPR001-201). Given that patients with CAH may require long-term treatment with SPR001, this study will investigate the extended use of SPR001 over a 3-month period in combination with replacement glucocorticoids and mineralocorticoids in the treatment of CAH.

2.2 Background

2.2.1 Congenital Adrenal Hyperplasia

CAH is a chronically debilitating autosomal recessive genetic disorder caused by a critical enzymatic deficiency in the steroidogenic pathways that synthesize the corticosteroids aldosterone and cortisol within the adrenal gland (White and Speiser, 2000; Bachelot et al, 2008). CAH is typically classified as either classic (the more severe form that is usually detected

in infancy) or nonclassic (the milder form that may not become evident until childhood or early adulthood). Classic CAH can be further sub-classified as salt-wasting or simple virilizing. Approximately 75% of CAH patients have a mutation that leads to severe aldosterone deficiency, resulting in the salt-wasting form of CAH characterized by the loss of large amounts of sodium via their urine (hyponatremia), hyperkalemia, and elevated plasma renin activity indicating hypovolemia, leading to dehydration and hypotension that can be life threatening in early infancy. The remaining 25% of CAH patients produce sufficient aldosterone to avoid neonatal adrenal crisis but are nevertheless debilitated by the simple virilizing form of CAH resulting from impaired cortisol production. Cortisol deficiency, a hallmark of CAH, disrupts the balance of the HPA axis by removing the negative feedback to the hypothalamus provided by normal levels of cortisol. This leads to the overproduction of CRF by the hypothalamus, the consequent overproduction of ACTH by the pituitary gland, and the resulting adrenal hyperplasia and overproduction of cortisol precursors by the adrenal gland. Because CAH patients are deficient in enzymatic activity that converts cortisol precursors to cortisol, these precursors are funneled into the biosynthetic pathway for adrenal androgens, leading to androgen overproduction. Androgen excess may result in precocious puberty; seborrhea; impaired fertility; irregular menses, amenorrhea, acne, hirsutism, and virilization in females; and TARTs in males.

The most common genetic cause of CAH, accounting for over 90% of cases, is mutation of the *CYP21A2* gene, which encodes the cytochrome P450c21 enzyme, commonly known as 21-hydroxylase, which is required for the synthesis of cortisol and aldosterone from the precursors 17-OHP and progesterone (White and Speiser, 2000; Bachelot et al, 2008; Auchus, 2015; Doleschall et al, 2014). Mutations in genes that encode other enzymes critical in steroidogenesis (*CYP17A1, HSD3B2, CYP11B1,* and *POR*) contribute to the remaining 5% to 10% of CAH cases (Turcu and Auchus 2015). Severe mutations that completely ablate 21-hydroxylase activity lead to the salt-wasting form of CAH. Milder mutations that result in even 1% to 2% residual 21-hydroxylase activity enable sufficient aldosterone production to avoid neonatal adrenal crisis and produce the simple virilizing form of CAH. Neonatal screening of 17-OHP to diagnose CAH is now performed in the United States and many other countries, with the goal of reducing mortality and morbidity due to salt-wasting adrenal crises in newborns (Falhammar et al, 2015). A 17-OHP level >300 nmol/L is indicative of untreated CAH, and the patient is then generally genotyped to confirm the diagnosis and to help determine treatment approaches (Falhammar et al, 2015; Choi et al, 2016).

Evidence-based treatment guidelines for CAH are only beginning to be developed (Reisch, 2015), and current overall treatment effectiveness for CAH patients is poor (Mnif et al, 2012; Bachelot et al, 2015). Current treatment for CAH is centered around providing pharmacologic (supraphysiologic) doses of glucocorticoids (e.g., hydrocortisone) to replace cortisol. In patients with the salt-wasting form of CAH, mineralocorticoids (e.g., fludrocortisone) are also used to replace aldosterone; before weaning, salt supplements (NaCl) are also provided to prevent a potentially lethal salt-losing crisis. The challenge in using glucocorticoid therapy to manage CAH lies in its narrow therapeutic window and in striking the difficult balance between hyperandrogenism and hypercortisolism. Up to 70% of patients with CAH are considered

outside the acceptable bounds of biochemical control (Han et al, 2014). Among patients with 21-hydroxylase deficiency treated with glucocorticoids, normal serum androstenedione has been shown to be achieved in only 36% of patients (Arlt et al, 2010). Under-treatment carries the risk of adrenal insufficiency and crisis (dehydration, hypotension, hypoglycemia) and allows androgen overproduction (precocious puberty, female virilization, TARTs, infertility). In contrast, over-treatment with glucocorticoids may suppress growth and cause iatrogenic Cushing's syndrome, producing such metabolic symptoms as hypertension, greater BMI, obesity, hypercholesterolemia, and insulin resistance. Over a lifetime, the treatment of patients with CAH shifts from an emphasis on normal childhood growth to pubertal development to adult fertility and long-term health concerns, including metabolic abnormalities, cardiovascular disease, osteoporosis, and overall diminished quality of life (Auchus, 2015; Arlt et al, 2010).

Numerous studies have documented diminished quality of life in patients with CAH (Han et al, 2013; Aulinas and Webb, 2014; Gilban et al, 2014; Hummel et al, 2016). Faced with the debilitating effects of the disease itself, ineffective treatment, and/or the severe side effects of long-term high-dose glucocorticoid treatment, CAH patients may develop depression and anxiety. Patients with CAH have increased mortality, with 1 study documenting a mean age of death of 41.2 years in patients with 21-hydroxylase deficiency. The causes of death were adrenal crisis (42%), cardiovascular disease (32%), cancer (16%), and suicide (10%) (Falhammar et al, 2014).

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

2.2.2 SPR001 for the Treatment of CAH

SPR001 is being studied for the treatment of CAH on the basis of its ability to antagonize CRF_1 receptors located on the pituitary gland, thereby reducing the hypothalamic drive of CRF on the pituitary, consequent ACTH overproduction by the pituitary, and consequent 17-OHP and androgen overproduction by the adrenal glands. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced reductions in ACTH and 17-OHP in subjects with CAH (Turcu et al, 2016). In vitro studies show that SPR001 binds to CRF_1 receptors with high affinity and specificity and blocks CRF_1-mediated receptor function.

The safety profile of SPR001 has been established in nonclinical toxicology studies and in 2 completed Phase 1 clinical studies in healthy volunteers. A Phase 2 study in subjects with CAH (Study SPR001-201) is currently ongoing.

2.2.3 Nonclinical Toxicology of SPR001

The nonclinical safety profile of study drug substance (SPN001) has been evaluated in repeat-dose range-finding and definitive toxicology studies in rats and dogs administered SPN001 orally once daily for up to 91 consecutive days at doses up to 2000 mg/kg/day. In rats, SPN001-related findings were limited to the testes at 2000 mg/kg/day and the liver of both sexes at 5, 20, and 2000 mg/kg/day. The no observed adverse effect level (NOAEL) for SPN001 in rats was considered to be 20 mg/kg/day in males and 2000 mg/kg/day in females. In dogs, SPN001-related findings were limited to the testes at 2000 mg/kg/day, the liver of both sexes at

70 and 2000 mg/kg/day, and the thyroid gland of both sexes at 2000 mg/kg/day. The NOAEL for SPN001 in dogs was considered to be 70 mg/kg/day in both sexes. All findings in both species were reversible following a 6-week washout period. Refer to Section 2.3.1 for a discussion of the potential liver, testicular, and thyroid risks associated with SPR001.

In reproductive and developmental toxicity studies, no adverse effects on fertility or early embryonic development were noted when SPN001-treated male rats (dosed at 5, 20, or 1000 mg/kg/day) were mated with untreated female rats or when SPN001-treated female rats (dosed at 20, 300, or 1000 mg/kg/day) were mated with untreated male rats. The NOAEL for SPN001 for male and female reproductive function was considered to be 1000 mg/kg/day. In an embryo-fetal development study conducted in rabbits (dosed at 30, 100, or 1000 mg/kg/day), developmental toxicity, which occurred concomitantly with maternal toxicity, was noted at 100 and 1000 mg/kg/day. Effects included increases in resorptions and post-implantation loss and corresponding reductions in litter sizes and live fetuses at 1000 mg/kg/day and lower fetal body weight, a greater number of multiple morphological alterations, and reduced ossification in some bones of the paws at 100 and 1000 mg/kg/day. The NOAEL for developmental toxicity was considered to be 30 mg/kg/day.

In a study conducted in juvenile rats administered SPN001 at 100, 300, or 1000 mg/kg/day for 7 weeks beginning on postnatal day 45 (comparable to a 12-year-old human), adverse effects were limited to microscopic findings in the testes of males at 1000 mg/kg/day. These findings included minimal or mild bilateral tubular degeneration within the seminiferous tubules and scattered focal loss of various cell types, often segmental within a tubule, that lacked stage or cell-type specificity. Corresponding minimal luminal debris and reduced sperm within the epididymides were also noted. The NOAEL for SPN001 in juvenile rats was considered to be 300 mg/kg/day in males and 1000 mg/kg/day in females.

In addition, a complete battery of standard genotoxicity tests consisting of in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay has been conducted. A bovine corneal opacity and permeability assay has also been conducted.

2.2.4 Clinical Experience with SPR001

In 2 completed Phase 1 studies, a total of 53 healthy adult subjects aged 21 to 64 years were treated with at least 1 dose of SPR001. The first-in-human study of SPR001 (Study I3C-FW-BLAA) evaluated single ascending doses of 2 mg to 800 mg. In this study, a small number of subjects experienced diarrhea and headache of mild or moderate severity. A subsequent study (Study I3C-FW-BLAB) evaluated repeat doses of 50 mg, 150 mg, or 200 mg SPR001 once daily for 14 consecutive days. A small number of subjects in the repeat-dose study experienced dyspnea, rhinorrhea, palpitations, and headache. The Phase 1 studies showed no clinically significant alterations in safety laboratory values, vital signs, or ECGs. SPR001 was well tolerated in healthy human subjects, with no SPR001-related SAEs / AEs leading to discontinuation or DLTs.

An ongoing Phase 2, open-label, proof-of-concept study (Study SPR001-201) is currently evaluating the safety and efficacy of SPR001 in adults with classic CAH. Cohort A of Study SPR001-201 has been completed, with 10 subjects receiving at least 1 dose of SPR001 and 9 subjects completing the cohort. Dosing for each subject in Cohort A was to start at 200 mg QD (for 14 days) and to escalate to 600 mg QD (for 14 days), then 1000 mg QD (for 14 days). Preliminary safety data from Cohort A shows SPR001 to be generally well tolerated through 600 mg QD and 4 weeks of dosing, with no SAEs, AEs leading to discontinuation, DLTs, or AESIs and no meaningful changes across clinical laboratory, ECGs, the Beck Depression Inventory-II (BDI-II) and C-SSRS, or physical examination findings. Refer to Section 2.3 for preliminary safety and efficacy data from Cohort A that speaks to the potential clinical risks and benefits of SPR001 as a treatment for CAH. In Cohorts B/C/D of this study, approximately 3 to 6 subjects are expected to be enrolled into each cohort with a 2-week treatment period. Study drug dosing will begin at 200 mg BID in Cohort B and may be adjusted in Cohorts C/D based on an adaptive multiple ascending dose design.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Reversible effects on liver function tests (LFTs) have been observed in the ongoing Phase 2 Study SPR001-201 at the highest dose tested (1000 mg QD), after a total of 6 weeks on study drug. In Cohort A of Study SPR001-201, 2 subjects with CAH administered 1000 mg QD for 2 weeks (following 2 weeks on 200 mg QD and 2 weeks on 600 mg QD) experienced transient ALT elevations. One subject experienced an ALT elevation of >5x ULN and another subject experienced a mild ALT elevation of 2.3x ULN. Both events resolved by the end of the follow-up period. Bilirubin levels remained within normal levels in both subjects. No LFT abnormalities were observed in the Phase 1 clinical studies, which treated healthy adults with single SPR001 doses of up to 800 mg and multiple SPR001 doses of up to 200 mg QD for 14 days. No LFT abnormalities were observed in subjects in Cohort A dosed at up to 600 mg QD after a total of 4 weeks on study drug (2 weeks on 200 mg QD and 2 weeks on 600 mg QD).

Reversible testicular/spermatocyte degeneration/atrophy was observed in rats and dogs treated with the highest dose of SPR001 in the definitive toxicology studies (2,000 mg/kg/day). However, male reproductive studies in rats showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, no meaningful effects on clinical laboratory markers of testicular function (luteinizing hormone [LH], follicle-stimulating hormone [FSH], inhibin B, and sex hormone–binding globulin [SHBG]) have been observed in healthy male volunteers in the Phase 1 studies or in male subjects with CAH in Cohort A of Study SPR001-201.

Effects on the thyroid gland (follicular hypertrophy secondary to hepatocellular hypertrophy) were noted in dogs treated for 91 days at 2,000 mg/kg/day in the definitive toxicology study. The clinical relevance of this secondary finding is presently unclear. Thyroid function was not evaluated in the Phase 1 studies, and no meaningful changes in thyroid function have been observed in Cohort A of Study SPR001-201.

2.3.2 Known Potential Benefits

Evidence from nonclinical and early clinical studies suggests that SPR001 is effective as a CRF_1 receptor antagonist, a mechanism of action that supports the clinical investigation of SPR001 for the treatment of CAH. This mechanism of action has been validated in a previous proof-of-concept study using a similar small-molecule CRF_1 receptor antagonist, which produced reductions in ACTH and 17-OHP in subjects with CAH (Turcu et al, 2016). Preliminary data from Cohort A of Study SPR001-201 show clinical evidence of CRF_1 receptor target engagement (reductions in ACTH) and reductions in key adrenal hormones (17-OHP and androstenedione) at all dose levels tested.

2.3.3 Assessment of Potential Risks and Benefits

Multiple study design elements have been incorporated to mitigate the potential risks of LFT laboratory abnormalities, testicular injury, and thyroid effects described in Section 2.3.1. Because these risks are all associated with higher doses of SPR001, study drug will initially be administered in this study at 400 mg QD, which is within the range of clinical precedence that has been safe and well tolerated. Additionally, clinical laboratory measures of liver chemistry, testicular function, and thyroid function will be assessed every 2 weeks throughout the treatment period of this study. Liver chemistry will be monitored by measuring ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and total and direct bilirubin. Testicular function will be monitored by measuring LH, FSH, inhibin B, and SHBG; performing scrotal ultrasounds; and conducting semen analysis. Thyroid function will be monitored via a thyroid panel that measures T3, T4, and thyroid-stimulating hormone (TSH). Finally, strict individual treatment stopping criteria for liver chemistry findings and a criterion for increased liver chemistry monitoring are in place (see Section 7.2.1 and Section 12.2).

The mild and reversible toxicologic effects of SPR001 on the male reproductive tract in nonclinical studies occurred in the context of animals with normal, rather than elevated, baseline hormone function. As a CRF_1 receptor antagonist, SPR001 is intended to reduce abnormally elevated ACTH and androgen levels. In nonclinical models where baseline hormone levels are within normal ranges, clinical benefits are not expected, and indeed, toxicities may be expected as a result of androgen reduction outside of the normal range. However, in patients with CAH, whose baseline ACTH and androgen levels are pathologically elevated, androgen reduction would be considered a positive, therapeutic effect.

The Sponsor believes that the benefit-to-risk profile of this study is favorable. Given the serious nature of CAH and the limitations and risks of chronic steroid therapy, new treatment modalities are needed for patients with CAH. Given 1) the acceptable safety and tolerability profile of SPR001 in healthy volunteers from the Phase 1 program and in subjects with CAH administered study drug at up to 600 mg QD in Cohort A of Study SPR001-201 and 2) the preliminary evidence of reductions in ACTH, 17-OHP, and androstenedione at all dose levels tested in Cohort A of Study SPR001-201, the Sponsor believes that the benefit-to-risk profile favors the continued investigation of SPR001 and the investigation of extended treatment with SPR001 for up to 3 months in subjects with CAH.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety of SPR001 in subjects with CAH	• AEs, SAEs, AEs leading to discontinuation/withdrawal, DLTs, and AESIs • Physical examination findings • Vital signs • Changes in ECG • Changes in clinical laboratory values • Changes in the C-SSRS and the HADS
Secondary	
• To evaluate the efficacy of SPR001 in subjects with CAH in terms of changes in hormones	• Changes in ACTH, 17-OHP, androstenedione, and testosterone
Exploratory	
• To evaluate the effect of SPR001 on QoL, metabolic parameters, exploratory adrenal hormones, and sex-specific outcomes in subjects with CAH	• Changes in QoL as measured using the SF-36, PGIC, bother score, and CAH signs and symptoms interview • Changes in fasting glucose, HbA1c, fasting insulin, and lipid profile • Changes in BW and BMI • Changes in exploratory adrenal hormones • Changes in TARTs and on semen analysis in male subjects • Changes in acne, hirsutism, and menstrual cyclicity in female subjects

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2 study of SPR001 for the treatment of classic CAH that will provide 12 weeks of open-label treatment to eligible subjects. To be eligible for this study, an individual must either have completed Study SPR001-201 or meet eligibility criteria for SPR001-naïve subjects (see Section 5.2). The expected duration of study participation for each subject is up to approximately 7 months. This includes a screening period of 12 weeks, a treatment period of 12 weeks, and a safety follow-up period of 30 days.

Initial subjects who enroll in this study will be treated with SPR001 at 400 mg QD during the treatment period. For subjects who enroll later on in this study, the dose strength may be increased or decreased (by no more than 2-fold) and/or the dose regimen may be adjusted (e.g., to BID dosing, a regimen being tested in Study SPR001-201). In general, subjects are expected to complete the study at the dose strength and on the dose regimen at which they started the study, unless they experience a clinically significant AE that would warrant a dose reduction.

An SRC will review the available safety, PK, and PD data from Study SPR001-201 Cohorts B/C/D and from this study on an ongoing basis and provide recommendations to the Sponsor, who will ultimately decide on any dosing adjustments in this study.

The Schedule of Activities is provided in Section 1.3. Study visits will occur every 2 weeks during the treatment period and should be scheduled for the morning, to accommodate 8am laboratory assessments. Study visits for screening and at Day 1 (baseline), Week 4, Week 8, and Week 12 (end of treatment) will be conducted as outpatient clinic visits. Study visits at Week 2, Week 6, and Week 10 may be conducted as either outpatient clinic visits or in-home visits by qualified study personnel. A final safety follow-up outpatient clinic visit will occur 30 days after the last dose of study drug.

To reduce subject burden, the final safety follow-up visit in Study SPR001-201 for subjects completing that study and rolling over into this study may coincide with the screening visit of this study (with any overlapping assessments conducted only once). Subjects who completed the final follow-up visit in Study SPR001-201 >3 months before screening in this study and subjects naïve to SPR001 must complete anew all specified screening assessments for this study. Subjects will maintain a stable dose and regimen of glucocorticoids throughout this study.

4.2 Scientific Rationale for Study Design

In the ongoing Phase 2 Study SPR001-201, subjects with CAH are treated for 2 weeks with any particular dose level of study drug. Given that patients with CAH may require long-term treatment with SPR001 to maintain antagonism of CRF_1 receptors in the face of 21-hydroxylase deficiency, a longer-term study of the safety and efficacy of SPR001 is required. This study extends the duration of SPR001 treatment to 12 continuous weeks at a constant dose. The

treatment period of 12 weeks was chosen based on the 3-month duration of the definitive toxicology studies in rats and dogs.

Individuals may qualify for this study as either SPR001-experienced or SPR001-naïve subjects. Individuals who previously received study drug by completing Study SPR001-201 may qualify for this study to receive an extended 12 weeks of study drug. SPR001-naïve individuals may also qualify directly for this study and will provide a bigger sample size for safety data. The Sponsor may decide to restrict later enrollment of SPR001-naïve individuals to those who exhibit certain clinically significant sequelae of hyperandrogenism due to CAH – TARTs in the case of male CAH patients and significant acne, hirsutism, and/or ovulatory dysfunction in the case of female CAH patients. This enriched population may enable better evaluation of exploratory efficacy endpoints to inform future studies of SPR001.

All SPR001-experienced subjects will undergo a washout period before starting study drug in this study. This washout period will include, at a minimum, the 30-day safety follow-up period in Study SPR001-201 and the 12-week screening period in this study. Thus, SPR001-experienced subjects will generally undergo a washout period of at least approximately 4 months between their last dose of study drug in Study SPR001-201 and their first dose of study drug in this study. Furthermore, all subjects coming from Cohort A of Study SPR001-201 will have undergone a washout period of >5 months, given the interval between the completion of Cohort A in early 2018 and the anticipated start date of this study. Based on preliminary population PK analysis of data from Study SPR001-201 Cohort A, a washout period of 32 to 44 days (approximately 5 to 7 times the terminal phase for SPR001) would allow for essentially complete elimination of SPR001.

The schedule of study visits every 2 weeks during the treatment period and the option for some study visits to be in-home visits provides an appropriate balance between closely monitoring subject safety / response to therapy and minimizing subject burden. The 30-day post-treatment washout period in this study allows for adequate safety follow-up and analysis of any HPA axis rebound after the last dose of study drug.

Subjects will take study drug with a meal or after consumption of a standardized snack in order to improve absorption of study drug, since the Phase 1 clinical studies showed minimal study drug absorption when subjects were dosed in a fasted state. Specific dose reduction criteria, strict individual treatment stopping criteria, and appropriate laboratory and medical assessments have been established to ensure subject safety.

4.3 Justification for Dose

Study drug will initially be administered in this study at 400 mg QD. Preliminary clinical data support the safety and potential PD effects of this dose.

A dose of up to 200 mg QD (for 14 days) was clinically assessed in the repeat-dose Phase 1 Study I3C-FW-BLAB in healthy subjects and was well tolerated in that study.

In the ongoing Phase 2 Study SPR001-201 in subjects with CAH, Cohort A has been completed. Dosing for each subject in Cohort A was to start at 200 mg QD (for 14 days) and to escalate to

600 mg QD (for 14 days), then 1000 mg QD (for 14 days). Preliminary data from Cohort A show evidence of CRF_1 receptor target engagement (reductions in ACTH) and reductions in key adrenal hormones (17-OHP and androstenedione) at all dose levels tested. Preliminary safety data from Cohort A show SPR001 to be generally well tolerated through 600 mg QD and 4 weeks of dosing, with no SAEs, AEs leading to discontinuation, DLTs, or AESIs and no meaningful changes across clinical laboratory, ECGs, BDI-II and C-SSRS, or physical examination findings. At 1000 mg QD and 6 weeks of dosing, transient elevations in ALT (without any elevations in bilirubin) were observed in 2 subjects (see Section 2.3.1). Thus, a dose of 400 mg QD is initially planned in this study because this dose lies within the dose range of clinical precedence that has both produced responses in key hormones and been safe and well tolerated.

For subjects who enroll later on in this study, the dose strength may be increased or decreased (by no more than 2-fold) and/or the dose regimen may be adjusted based on ongoing review of the available safety, PK, and PD data from Study SPR001-201 Cohorts B/C/D and from this study by an SRC. For example, the dose regimen may be adjusted to BID dosing, a regimen being tested in Study SPR001-201 that may lower C_{max} levels, reduce peak-to-trough fluctuation, and improve diurnal control of elevated hormones in subjects with CAH relative to once-daily dosing.

4.4 End of Study Definition

A subject is considered to have completed the study if the subject has completed all 12 weeks of treatment. The end of the study is defined as the date of the last follow-up visit of the last subject in the study.

5 STUDY POPULATION

This study will enroll up to approximately 24 eligible subjects with classic CAH who either previously completed Study SPR001-201 (see Section 5.1) or meet eligibility criteria for SPR001-naïve subjects (see Section 5.2). The study will be conducted at approximately 8 investigative sites in the United States.

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.

5.1 Eligibility Criteria for Subjects Who Completed Study SPR001-201

5.1.1 Inclusion Criteria for Subjects Who Completed Study SPR001-201

Subjects who completed Study SPR001-201 must meet all of the following criteria to be eligible for this study:

1. Is approved by the Sponsor's Medical Monitor
2. Is on a stable regimen of glucocorticoid replacement for ≥12 weeks before baseline that is expected to remain stable throughout the study
3. If screening for this study occurs >3 months after the subject's final follow-up visit in Study SPR001-201, the subject will have serum 17-OHP measured at screening. On the day of screening, the subject should take any morning glucocorticoid medication after the screening blood draw to allow for an unimpeded assessment of 17-OHP. The subject will be included if screening shows 17-OHP ≥800 ng/dL.
4. Agrees to follow contraception guidelines (Section 5.3.5). Male subjects must also agree to refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug.
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

5.1.2 Exclusion Criteria for Subjects Who Completed Study SPR001-201

Subjects who completed Study SPR001-201 will not be eligible for this study if they meet any of the following criteria:

1. Experienced a clinically significant AE (defined in Section 7.2.7) considered at least possibly related to SPR001 in Study SPR001-201
2. If screening for this study occurs >3 months after the subject's final follow-up visit in Study SPR001-201, the subject will be screened for any clinically significant unstable medical condition, medically significant illness, or chronic disease occurring within 30 days of screening, including but not limited to the following:

a. A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
b. Presence of clinically significant renal disease, as evidenced by an eGFR of <60 mL/min/1.73 m^2
c. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
d. Confirmed positive test at screening for active hepatitis B, hepatitis C, or HIV

3. If screening for this study occurs >3 months after the subject's final follow-up visit in Study SPR001-201, the subject will be screened for clinically significant psychiatric disorders by history and from the M.I.N.I. conducted at screening. The subject will be excluded if screening reveals evidence of current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months.
4. Is at increased risk of suicide on the basis of the Investigator's judgment or the results of the C-SSRS conducted at screening and baseline (e.g., C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)
5. Has a HADS score >12 for either depression or anxiety at screening or baseline
6. Clinically significant abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:
    a. Clinically meaningful abnormal ECG results, in the opinion of the Investigator
    b. QTcF >450 msec for male participants or >470 msec for female participants
    c. ALT >2x ULN
    d. Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
7. Subjects who routinely work overnight shifts require Medical Monitor approval for enrollment
8. Females who are pregnant or lactating
9. Use of any other investigational drug within 30 days or 5 half-lives (whichever is longer) before screening
10. Use of prohibited concomitant medications (see Section 6.5.2.1), including rosiglitazone, testosterone, and strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids and birth control), within 30 days or 5 half-lives (whichever is longer) of baseline. Medications metabolized by CYP3A4, 2C8, 2C9, or 2C19, especially those that are sensitive substrates or substrates with narrow therapeutic ranges (see Section 6.5.2.2), should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If

washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before baseline.

11. Donation of blood within 60 days before baseline or donation of platelets, white blood cells, or plasma within 15 days before baseline

5.2 Eligibility Criteria for SPR001-Naïve Subjects

This study will offer enrollment to SPR001-naïve subjects with eligibility criteria similar to those of Study SPR001-201 but will also seek to include an enriched population of subjects with CAH who exhibit clinically significant sequelae of androgen excess, specifically males 18 to 35 years old with TARTs and adult females with clinically significant acne, hirsutism, and/or ovulatory dysfunction. This study will initially allow enrollment of at least 3 subjects who meet general eligibility criteria for all SPR001-naïve subjects (inclusion criteria in Section 5.2.1 and exclusion criteria in Section 5.2.3) and who may or may not meet additional inclusion criteria for an enriched population of SPR001-naïve subjects. At any time thereafter, the Sponsor may decide to require all SPR001-naïve subjects who enroll subsequently to satisfy the additional inclusion criteria for an enriched population of SPR001-naïve subjects (Section 5.2.2). In particular, the study will attempt to enroll an enriched subpopulation of up to approximately 8 male subjects 18 to 35 years old with TARTs, subject to the limitations of enrollment feasibility for this subpopulation and with consideration for the total number of accrued subjects in the study.

5.2.1 General Inclusion Criteria for All SPR001-Naïve Subjects

All SPR001-naïve subjects must meet all of the following criteria to be eligible for this study:

1. Male and female subjects ≥18 years old
2. Has a documented historical diagnosis of classic CAH due to 21-hydroxylase deficiency based on documented genetic mutation or elevated 17-OHP
3. Known or suspected differential diagnosis of any of the other known forms of CAH, including non-classic CAH, requires Medical Monitor approval for enrollment
4. Has serum 17-OHP ≥800 ng/dL at screening. On the day of screening, the subject should take any morning glucocorticoid medication after the screening blood draw to allow for an unimpeded assessment of 17-OHP.
5. Is on a stable regimen of glucocorticoid replacement for ≥12 weeks before baseline that is expected to remain stable throughout the study
6. Agrees to follow contraception guidelines (Section 5.3.5). Male subjects must also agree to refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study drug.
7. Is able to understand all study procedures and risks involved and provides written informed consent indicating willingness to comply with all aspects of the protocol

5.2.2 Additional Inclusion Criteria for Enriched Population of SPR001-Naïve Subjects

After an initial enrollment of at least 3 SPR001-naïve subjects who must fulfill only the inclusion criteria in Section 5.2.1, the Sponsor may decide to require all SPR001-naïve subjects who enroll subsequently to satisfy all of the following additional inclusion criteria for an enriched population of SPR001-naïve subjects:

1. If male, must be 18 to 35 years old, inclusive.
2. If male, must have a diagnosis of TART(s) confirmed via scrotal ultrasound at screening with at least 1 lesion having a diameter ≥4 mm
3. If female, must have at least one of the following clinically significant sequelae of androgen excess:
    a. Clinically significant acne defined as an IGA score ≥2 at screening
    b. Clinically significant hirsutism defined as an mFG score ≥6 at screening
    c. Verifiable history (based on medical records or ability to obtain an accurate history from the individual) of ovulatory dysfunction defined as having at least 1 year of menstrual cycles that last ≥45 days or having ≤8 menstrual periods within the past year, if the subject is not on a hormonal contraceptive

5.2.3 Exclusion Criteria for All SPR001-Naïve Subjects

SPR001-naïve subjects will not be eligible for this study if they meet any of the following criteria:

1. Has had a clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
    a. A malignancy or <3 years of remission history from any malignancy, other than successfully treated localized skin cancer
    b. Presence of clinically significant renal disease, as evidenced by an eGFR of <60 mL/min/1.73 m^2
    c. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
    d. Confirmed positive test at screening for active hepatitis B, hepatitis C, or HIV
2. Had or has a clinically significant psychiatric disorder either by history or from the M.I.N.I. conducted at screening. The subject will be excluded if screening reveals evidence of current major depressive episode, bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, or any other psychotic disorder within the preceding 6 months.
3. Is at increased risk of suicide on the basis of the Investigator's judgment or the results of the C-SSRS conducted at screening and baseline (e.g., C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months)
4. Has a HADS score >12 for either depression or anxiety at screening or baseline

5. Clinically significant abnormal clinical or laboratory assessments must be discussed with the Medical Monitor to determine eligibility for this study. Abnormal assessments that must be reviewed to determine eligibility include but are not limited to:
    a. Clinically meaningful abnormal ECG results, in the opinion of the Investigator
    b. QTcF >450 msec for male participants or >470 msec for female participants
    c. ALT >2x ULN
    d. Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
6. Has a history that includes bilateral adrenalectomy or hypopituitarism
7. Subjects who routinely work overnight shifts require Medical Monitor approval for enrollment
8. Females who are pregnant or nursing
9. Use of any other investigational drug within 30 days or 5 half-lives (whichever is longer) before screening
10. Use of prohibited concomitant medications (see Section 6.5.2.1), including rosiglitazone, testosterone, and strong inhibitors and/or inducers of CYP3A4 (with the exception of glucocorticoids and birth control) within 30 days or 5 half-lives (whichever is longer) of baseline. Medications metabolized by CYP3A4, 2C8, 2C9, or 2C19, especially those that are sensitive substrates or substrates with narrow therapeutic ranges (see Section 6.5.2.2), should be discussed on a case-by-case basis with the Medical Monitor to determine whether the medication should be discontinued or may be continued with caution. If washout is feasible, then the medication should be withdrawn at least 30 days or 5 half-lives (whichever is longer) before baseline.
11. Donation of blood within 60 days before baseline or donation of platelets, white blood cells, or plasma within 15 days before baseline

5.3 Lifestyle Considerations

5.3.1 Shift Work

Given the daily dosing of SPR001 at 10pm during the treatment period and the blood draws for laboratory assessments at 8am on study visit days, subjects who routinely work overnight shifts require Medical Monitor approval before enrollment.

5.3.2 Meals and Dietary Restrictions

Study drug must be consumed with a meal or 5 to 15 minutes after a standardized snack. Standardized snacks will be provided for all dosing days. A list of acceptable alternative food combinations will also be provided.

Subjects will be advised to refrain from consumption of grapefruit or grapefruit juice from 1 day before the first dose of study drug in this study until after the final dose.

5.3.3 Caffeine, Alcohol, and Tobacco

For study visits with 8am blood draws, subjects should abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, or chocolate) from 5 hours before the blood draw (3am) until after the blood draw. Subjects will abstain from alcohol from 12 hours before the blood draw (8pm) until after the blood draw.

Subjects who use tobacco products should be informed that nicotine-containing products are not permitted while they are at the investigational site.

5.3.4 Activity

Subjects should abstain from strenuous exercise for 8 hours before each study visit.

5.3.5 Contraception Guidelines

5.3.5.1 Contraception Guidelines for Male Subjects

A male enrolling in this study who has a female partner of childbearing potential, including those who are breastfeeding, must meet ONE of the following contraceptive criteria:

1. Is sexually abstinent from penile-vaginal intercourse as his usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent throughout the duration of the study
2. Is vasectomized and the absence of sperm has been confirmed
3. Agrees to use a male condom plus partner use of one of the following highly effective contraceptive methods for the duration of the study:
    a. Combined hormonal contraception (containing estrogen and progestogen): oral, intravaginal, or transdermal
    b. Progestogen-only hormonal contraception: oral, injectable, or implantable intrauterine device (IUD) or intrauterine system (IUS)
    c. Bilateral tubal occlusion

5.3.5.2 Contraceptive Guidelines for Female Subjects

A female enrolling in this study must meet ONE of the following contraceptive criteria:

1. Is postmenopausal

    A postmenopausal state is defined as no menses for at least 1 year without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, a single FSH measurement is insufficient to establish a postmenopausal state without at least 1 year of amenorrhea.
2. Is premenopausal but has documentation of one of the following:
    a. Hysterectomy
    b. Bilateral salpingectomy
    c. Bilateral oophorectomy

3. Has only 1 male sexual partner, that partner is vasectomized, and the absence of sperm has been confirmed
4. 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 throughout the duration of the study
5. Agrees to use one of the following highly effective contraceptive methods for the duration of the study:
    a. Combined hormonal contraception (containing estrogen and progestogen): oral, intravaginal, or transdermal
    b. Progestogen-only hormonal contraception: oral, injectable, or implantable IUD or IUS
    c. Bilateral tubal occlusion

5.4 Screen Failures

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

Individuals who do not meet the following criteria for participation in the study may be rescreened according to the following guidelines after consultation with the Sponsor's Medical Monitor:

- Individuals who do not meet the screening 17-OHP inclusion criterion may be rescreened after 30 days if their glucocorticoid replacement dose is reduced for clinical reasons. Any morning dose of glucocorticoid medication should be taken after the screening blood draw to allow for an unimpeded assessment of 17-OHP.
- Individuals on incompatible or excluded concomitant medications may be rescreened after an appropriate washout period (e.g., 30 days or 5 half-lives, whichever is longer).

6 STUDY INTERVENTION

6.1 Study Intervention Administration

6.1.1 Study Intervention Description

SPR001 is a small-molecule CRF_1 receptor antagonist.

Details about the physical, chemical, and pharmaceutical properties of SPR001 are provided in the IB.

6.1.2 Dosing and Administration

Initial subjects who enroll in this study will be treated with oral study drug at 400 mg QD at 10pm for 12 weeks. This dose is within the range of doses that were well tolerated and reduced key hormones (ACTH, 17-OHP, and androstenedione) in subjects with CAH in Cohort A of Study SPR001-201. For subjects who enroll later on in this study, the dose strength may be increased or decreased (by no more than 2-fold) and/or the dose regimen may be adjusted (e.g., to BID dosing, a regimen being tested in Study SPR001-201). In general, subjects are expected to complete the study at the dose strength and on the dose regimen at which they started the study, unless they experience a clinically significant AE that would warrant a dose reduction. An SRC will review the available safety, PK, and PD data from Study SPR001-201 Cohorts B/C/D and from this study on an ongoing basis and provide recommendations to the Sponsor, who will ultimately decide on any dosing adjustments in this study.

Only authorized site staff may dispense study drug. Sites will provide subjects with dosing instructions. Subjects being treated with study drug at 400 mg QD will be instructed to take 2 capsules daily at 10pm. If dosing is adjusted to a BID regimen, subjects will be instructed on when to take study drug in the morning and in the evening. If a subject goes to bed earlier than 10pm, the subject will take the 10pm dose of study drug at bedtime. Study drug will be taken with a meal or 5 to 15 minutes after consumption of a standardized snack. If a morning dose of study drug is added and a subject wishes to take his/her morning dose of study drug with breakfast, the Investigator should discuss the specific dosing situation with the Sponsor's Medical Monitor. If a morning dose of study drug is added, subjects should hold off on taking their morning dose of study drug on the mornings of all applicable study visits until after laboratory assessments have been completed. On all other days during the treatment period, subjects should take their morning dose of study drug at their usual time.

Instructions for concomitant glucocorticoid medication dosing are provided in Section 6.5.1. Instructions for study drug dose reduction are provided in Section 7.1. Criteria for study drug discontinuation are provided in Section 7.2.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

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

6.2.2 Formulation, Appearance, Packaging, and Labeling

The drug product SPR001 is formulated as a white, hard-gelatin capsule containing either 50 mg or 200 mg of the drug substance SPN001 in powder form with no excipients.

Study drug capsules containing 50 mg SPN001 are size 4 and will be packaged with 32 capsules per bottle in a 30-mL high-density polyethylene (HDPE) bottle with a 28-mm child-resistant cap and an induction foil seal.

Study drug capsules containing 200 mg SPN001 are size 1 and will be packaged with either 14 capsules per bottle (in a 30-mL HDPE bottle with a 28-mm child-resistant cap and an induction foil seal) or with 60 capsules per bottle (in a 75-mL HDPE bottle with a 33-mm child-resistant cap and an induction foil seal).

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

6.2.3 Product Storage and Stability

Study drug capsules are stable when stored at room temperature (20 °C to 25 °C) but should be protected from light. 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 site staff.

6.3 Treatment Assignment

Initial subjects who enroll in this study will be treated with study drug at 400 mg QD. This dose strength and/or dose regimen may be adjusted for subjects who enroll later on in this study based on ongoing review of the available safety, PK, and PD data from Study SPR001-201 Cohorts B/C/D and from this study by an SRC.

6.4 Study Intervention Compliance

Subject compliance will be assessed by maintaining adequate study drug dispensing records. Subjects will return bottles of study drug at each visit for a pill count. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol.

6.5 Concomitant Therapy

Concomitant medication is any medication (including over-the-counter [OTC] medication, prescription medication, vaccines, vitamins, and supplements) that the subject is receiving at screening or receives during the study. 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 12.1. Subjects should be instructed to contact the site immediately any time a new medication is required during the course of the study, including prescription and OTC medications, even those to be used for only a short period of time (e.g., antibiotics, cold and flu remedies, gastrointestinal therapies, opioids or other pain relievers). The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Glucocorticoid Replacement Therapy

Subjects must be on a stable regimen of glucocorticoid replacement therapy for ≥12 weeks before baseline to be eligible for this study. Changes in glucocorticoid dosing during the study are discouraged, and any changes will be recorded.

On the mornings of all study visits, including screening, subjects should hold off on taking any morning dose of glucocorticoid medication until after laboratory assessments are completed. On all other days during the study, subjects may take any morning glucocorticoid medication at their usual time.

6.5.2 Prohibited Concomitant Medications and Concomitant Medications of Concern

Section 12.1 outlines medications that are either prohibited or must be used with caution because of their potential for metabolic interactions with SPR001. 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. If a medication is to be washed out, it should be stopped at least 30 days or 5 half-lives, whichever is longer, before the first dose of SPR001 in this study and cannot be resumed until after the safety follow-up visit. In many cases, washout will necessitate rescreening. If a prohibited medication such as an antibiotic or antifungal agent is required during a subject's study participation, the Medical Monitor should be consulted to discuss appropriate actions, such as the temporary withholding of SPR001 until treatment with the prohibited agent is completed.

6.5.2.1 Prohibited Concomitant Medications

Other investigational drugs are prohibited during the study.

Rosiglitazone treatment is prohibited during the study because it could affect the subject's ACTH levels. Treatment with testosterone is also prohibited. In general, subjects who require ongoing treatment with rosiglitazone or testosterone should not be screened.

In vitro cytochrome P450 (CYP) reaction phenotyping has indicated that SPN001 is metabolized by CYP3A4. Therefore, drugs that are known strong inducers or inhibitors of CYP3A4 are generally prohibited during the study and require a washout period before screening. Stable daily doses of glucocorticoids and birth control are not restricted.

Specifically prohibited concomitant medications are listed in Section 12.1.1.

6.5.2.2 Concomitant Medications of Concern

In vitro metabolism studies have indicated that SPN001 has the potential to inhibit CYP3A4, 2C8, 2C9, and 2C19. Therefore, drugs metabolized by CYP3A4, 2C8, 2C9, and/or 2C19 should be avoided or used with caution, especially drugs that are sensitive substrates of these enzymes or that have narrow therapeutic ranges. Sensitive CYP substrates are drugs whose plasma area under the curve (AUC) has been shown to increase ≥5-fold when co-administered with a known CYP inhibitor and drugs for which the AUC in poor metabolizers is >5-fold the AUC in extensive metabolizers. Drugs with narrow therapeutic ranges are those for which even small increases in a subject's exposure to these drugs (potentially induced by the concomitant use of the CYP inhibitor SPR001) could lead to serious safety concerns (e.g., torsades de pointes).

Whenever feasible, subjects will discontinue use of a medication of concern and undergo a washout period before screening. However, if washout is not feasible, the Investigator should consult with the Medical Monitor to decide on the best course of action. If a medication of concern is to be continued, it must be used with caution and the subject must be carefully followed.

Specific concomitant medications of concern are listed in Section 12.1.2.

It is important to note that many commonly used medications are listed as drugs of concern, including certain statins (lovastatin, simvastatin), anti-inflammatory agents (celecoxib, felodipine), migraine remedies (ergotamine, dihydroergotamine, eletriptan), anxiolytics (buspirone, clobazam, midazolam), and drugs for erectile dysfunction (avanafil, sildenafil, vardenafil). Subjects must be willing to refrain from the use of these erectile dysfunction drugs during the study. It is critical that each subject's concomitant medications are carefully compared to the list.

7 DOSE REDUCTION, STUDY DRUG DISCONTINUATION, AND PARTICIPANT WITHDRAWAL

7.1 Dose-Limiting Toxicity and Dose Reduction

A DLT is defined as a Grade 3 or higher TEAE considered at least possibly related to study drug. If a subject experiences a DLT, the Investigator may reduce the subject's daily dose of SPR001 (by 50 to 200 mg), depending on the TEAE, in order to keep the subject on study. A Grade 3 or higher TEAE considered related to study drug will also be considered an AESI (see Section 8.2.8). Potential dose reductions must be discussed with the Medical Monitor. At any time during the study, subjects who experience any clinically significant signs of acute adrenal insufficiency (e.g., postural hypotension, nausea, abdominal pain) may have their study drug dose reduced or withheld and/or their glucocorticoid replacement therapy modified (see Section 7.2.4).

7.2 Study Drug Discontinuation

Subjects may voluntarily discontinue study drug or the Investigator may discontinue a subject's study drug at any time. 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 clinically significant liver chemistry, QTcF, or other individual treatment stopping criteria described in this section. Subjects may discontinue study drug but remain in the study for follow-up.

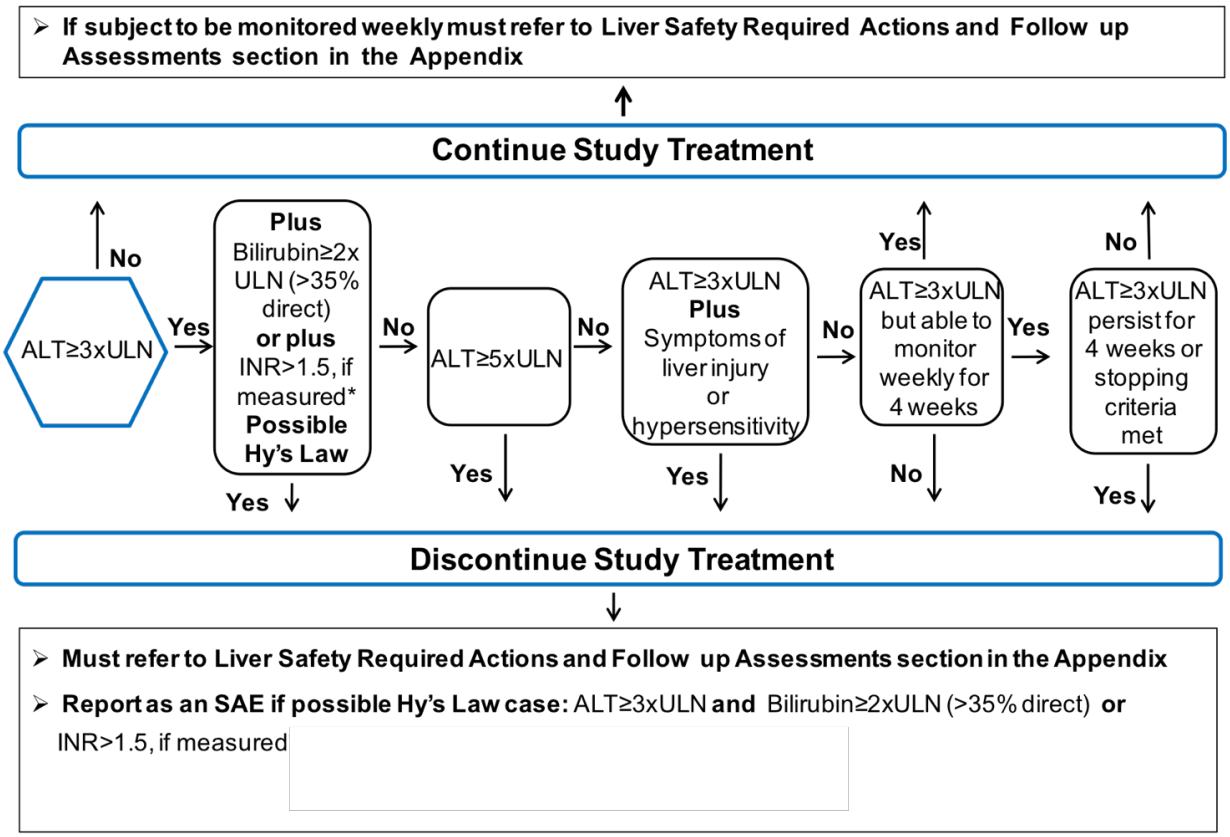
If study drug is discontinued, the Investigator will report the discontinuation to the Medical Monitor, document the date and reason for study drug discontinuation on the appropriate electronic case report form (eCRF), schedule an early termination visit for the subject (see the Schedule of Activities in Section 1.3), 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.

7.2.1 Liver Chemistry Stopping Criteria

Liver chemistry stopping criteria schematized in Figure 1 are designed to ensure subject safety and to evaluate liver event etiology. Suggested actions and follow-up assessments are provided in Section 12.2. A significant change in liver chemistry that does not satisfy stopping criteria may still be considered an AESI (see Section 8.2.8).

Figure 1. Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



7.2.2 QT Stopping Criteria

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

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

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

7.2.3 Suicidality Stopping Criteria

SPR001 is considered to be a central nervous system (CNS)–active study drug. Some CNS-active drugs may be associated with an increased risk of suicidal ideation in certain populations. Although SPR001 has not been shown to be associated with an increased risk of suicidal thinking or behavior when given to healthy volunteers, subjects will be monitored for such events during this study using the C-SSRS (see Section 8.1.6.1).

Individuals who provide a positive answer to question 3, 4, or 5 of the C-SSRS (on suicidal ideation) at screening or baseline are not eligible for this study. The Investigator should immediately contact the Medical Monitor to discuss possible study drug discontinuation and appropriate safety follow-up for a subject who provides a positive answer to question 3, 4, or 5 of the C-SSRS at any visit after baseline. This will also be considered an AESI (see Section 8.2.8).

The subject's HADS score should also be evaluated in conjunction with the C-SSRS (see depression stopping criteria in Section 7.2.5).

7.2.4 Adrenal Insufficiency Stopping Criteria

If a subject dosed with study drug exhibits clinically significant signs of acute adrenal insufficiency, such as postural hypotension, nausea, and abdominal pain, the Investigator should consider withholding the subject's dose(s) of SPR001, initiate appropriate corticosteroid therapy, and contact the Medical Monitor. If there is no clear explanation for the subject's acute adrenal insufficiency, such as inadequate corticosteroid replacement dosing or low circulating levels of plasma cortisol, the Investigator should review the subject with the Medical Monitor for possible study drug discontinuation.

7.2.5 Depression Stopping Criteria

Individuals who score >12 on either the depression or anxiety subscale of the HADS (see Section 8.1.6.2) at screening or baseline are generally not eligible for this study. The Investigator should immediately contact the Medical Monitor to discuss possible study drug discontinuation and appropriate safety follow-up for a subject who scores >12 on either the depression or anxiety subscale of the HADS at any visit after baseline. This will also be considered an AESI (see Section 8.2.8). Reasons for an elevated HADS score (aside from clinical depression) include chronic pain and stress.

7.2.6 Reproductive Hormone Stopping Criteria

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

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

7.2.7 Potentially Clinically Significant Adverse Events

Clinically significant AEs include but are not limited to SAEs (Section 8.2.2), AEs leading to study drug discontinuation/study withdrawal, DLTs (Section 7.1), and AESIs (Section 8.2.8) that are each considered at least possibly related to study drug. The occurrence of any clinically

significant AE will receive special consideration in decisions regarding continuation or suspension of dosing or enrollment and will be reported to the SRC within 1 day of awareness for immediate review.

Section 12.3 also provides a list of signs and symptoms (Section 12.3.1) and a list of laboratory findings (Section 12.3.2) that constitute potentially clinically significant AEs not otherwise specified among the foregoing individual treatment stopping criteria. These provide guidelines for a level of moderate-severe abnormality in safety findings that could cause harm to subject health and may preclude further study drug dosing. These lists are intended to guide the Investigator and are not meant to be a set of absolute criteria. Safety parameters not included in the list may be interpreted in a similar fashion according to Investigator judgment. Common Terminology Criteria for Adverse Events (CTCAE) severity grading should also be referenced (Section 8.2.3.1).

7.3 Participant Withdrawal from the Study

Subjects may voluntarily withdraw from the study or be withdrawn by the Investigator at any time. If a subject withdraws from the study, the Investigator must document the date and primary reason for the withdrawal on the appropriate eCRF.

Reasons for a subject to discontinue study drug or to withdraw from this clinical study include but are not limited to the following:

- Withdrawal of informed consent
- Fulfilling individual treatment stopping criteria (see Section 7.2).
- AE(s)
- Protocol deviation or noncompliance with study procedures/restrictions
- Desire or need to start a contraindicated therapy or another therapy for CAH
- Study termination by the Sponsor
- Lost to follow-up

7.4 Lost to Follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject, including, where possible, making 3 telephone calls to the subject and, if necessary, sending a certified letter to the

subject's last known mailing address (or local equivalent methods). Attempts to contact the subject should be documented in the subject's medical record.

- If the subject continues to be unreachable, the subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

This section describes what study assessments and procedures will be performed and how they will be conducted. The timing of study assessments and procedures is provided in the Schedule of Activities in Section 1.3.

8.1 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs (including SAEs, AEs leading to discontinuation/withdrawal, DLTs, and AESIs), physical examination, vital signs assessment, ECGs, clinical laboratory, and monitoring for suicide risk and depression/anxiety. AE procedures are described in Section 8.2.

8.1.1 Physical Examination

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

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

As part of both the full and abbreviated physical examinations, female subjects will be asked about the date, duration, and nature of their last menstrual period.

As part of the examination of the skin where specified in the Schedule of Activities, acne will be evaluated in all subjects and hirsutism will be evaluated in female subjects. Acne severity will be graded using an Investigator's Global Assessment (IGA) score per FDA guidance. Hirsutism will be graded using a modified Ferriman Gallwey (mFG) score (Yildiz et al, 2010; Martin et al, 2018). The mFG scores each of 9 body areas on a scale of 0 (no hair) to 4 (hairiness typical of a man), with the sum of the separate scores providing a hormonal hirsutism score.

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

8.1.2 Vital Signs

Vital signs consist of systolic and diastolic blood pressure, pulse rate, respiration rate, and body temperature. Vital signs will be measured as specified in the Schedule of Activities and as clinically indicated.

8.1.3 Body Weight, Height, and BMI

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

Height needs to be recorded at Visit 1 only.

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

8.1.4 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 Fridericia's formula. Any ECG measurement assessed by the Investigator as a clinically significant abnormality should be recorded in the AE section of the eCRF and monitored until resolution.

Refer to Section 7.2.2 for QT individual treatment stopping criteria and any additional ECGs that may be necessary.

8.1.5 Clinical Laboratory

A list of study-required clinical laboratory tests is provided in Section 12.4. A list of potentially clinically significant laboratory findings is provided in Section 12.3.2.

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 repeated at least weekly until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

8.1.6 Psychiatric Evaluations

8.1.6.1 Columbia–Suicide Severity Rating Scale

The C-SSRS will be used during the study to monitor suicidal ideation and behavior. The C-SSRS is a Food and Drug Administration (FDA)–endorsed questionnaire administered by trained study personnel to screen for suicidality 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.

In addition, subjects should be observed closely, and families and caregivers of subjects should be instructed to monitor subjects for suicidal ideation and behavior or any other unusual changes in behavior. Any such symptoms should be reported immediately to the Investigator.

Refer to Section 7.2.3 for suicidality individual treatment stopping criteria.

8.1.6.2 Hospital Anxiety and Depression Scale

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

Refer to Section 7.2.5 for depression individual treatment stopping criteria.

8.2 Adverse Events and Serious Adverse Events

8.2.1 Definition of Adverse Event

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

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

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

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

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

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

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported 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 of the AE.

8.2.2 Definition of Serious Adverse Event

An SAE or serious adverse drug reaction (ADR) 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. 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.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Hospitalization does not include the following:

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

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

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for workup of persistent pre-treatment lab abnormality)
- Social admission (e.g., subject has no place to sleep)
- Administrative admission (e.g., for yearly physical exam)

- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject

8.2.3 Classification of an Adverse Event

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

- Duration (start and end dates)
- Severity grade (Section 8.2.3.1)
- Relationship to study drug (Section 8.2.3.2)
- Action(s) taken and, as relevant, the outcome (Section 8.2.3.3)

8.2.3.1 Severity

The severity of each AE will be graded according to the National Cancer Institute (NCI) CTCAE version 4.03, which is summarized in Table 1.

Table 1. 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.

If there is an increase in the severity of an ongoing AE, it will be recorded as part of the same event, with the worst grade of severity recorded.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed in Section 8.2.2.

8.2.3.2 Relationship to Study Drug

The Investigator must provide an assessment of causality for all AEs, both serious and non-serious, that serves to determine whether there exists a reasonable possibility that the study drug caused or contributed to the AE. The Investigator will assess the relatedness of each AE to study drug according to the categories in Table 2. AEs classified as unrelated or unlikely related to study drug will be considered not related to treatment, and AEs classified as possibly, probably, or definitely related to study drug will be considered related to treatment.

Table 2. 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 (e.g., as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the study drug.
DEFINITELY RELATED: This category applies to those AEs that the Investigator thinks are incontrovertibly related to the study drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence in relation to administration of the study drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) it disappears or decreases upon cessation or reduction in dose of study drug and recurs with re-exposure to the study drug (if re-challenge occurs); and (4) it follows a known pattern of response to the study drug.

Abbreviation: AE, adverse event.

8.2.3.3 Outcome

The outcome of each AE will be recorded as one of the categories in Table 3.

Table 3. Outcome of Adverse Event

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

Abbreviation: AE, adverse event.

8.2.4 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 should be recorded but will not be considered TEAEs. If the AE occurs on the date of the first dose of study drug, the time of onset will be captured to determine whether the AE occurred before or after study drug administration.

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event has been shown to be unrelated to study drug, or the subject is lost to follow-up (as defined in Section 7.4).

8.2.5 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 8.2.4 and according to classifications described in Section 8.2.3.

Non-serious AEs that don't require immediate reporting are to be reported on the AE eCRF. AEs that lead to permanent discontinuation of study drug must also be reported separately on the appropriate eCRF.

SAEs and other potentially clinically significant AEs will receive special consideration in decisions regarding continuation or suspension of dosing or enrollment and will be reported to the SRC within 1 day of awareness for immediate review. Refer to Section 8.2.6 for reporting of SAEs. Refer to Section 7.2.7 for information on clinically significant AEs.

8.2.6 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. 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. 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.

Information about SAEs will be recorded on the SAE Report Form and sent to the Sponsor via fax or email using the contact information provided on the form. SAEs must be clearly differentiated from other types of events through the usage of the SAE Report Form. The SAE Report Form and completion guidelines are provided in the Investigator Site File. The Investigator must assess and record the relationship of each event to the study drug. SAEs must also be captured in the eCRF.

Any follow-up information provided should indicate that the information is follow-up to a previously reported SAE. Follow-up information should describe whether the event resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

8.2.7 Reporting of Pregnancy

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

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

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

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

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

8.2.8 Adverse Events of Special Interest

AESIs are those AEs that do not meet SAE criteria but must be monitored on an ongoing basis. These events will be reported on the SAE Report Form, allowing for the collection of additional information, as warranted. The following will be considered AESIs for this study:

- Suicidality as indicated by type 3, 4, or 5 ideation on the C-SSRS (see Section 7.2.3 regarding study drug stopping criteria and Section 8.1.6.1 regarding the C-SSRS). This should be reported as an AESI until it becomes serious according to the SAE definition (e.g. hospitalization).
- High HADS score or other indication of worsening depression (see Section 7.2.5 regarding study drug discontinuation and Section 8.1.6.2 regarding the HADS)
- Significant liver chemistry changes that do not satisfy stopping rules (see Section 7.2.1 and Section 12.2.1). Cases of Hy's Law should be reported as SAEs.
- Severity Grade 3 or higher TEAE considered related to study drug (see Section 7.1 regarding dose reduction)

8.2.9 Disease-Related Events

The following disease-related events are common in patients with CAH, and this should be taken into consideration when evaluating the causality of AEs during the study:

- Acute encephalopathy
- Adrenal crisis or insufficiency
- Avascular necrosis
- Memory impairment
- Dizziness
- Dyslipidemia; hyperlipidemia
- Dyspepsia
- Elevated fasting serum leptin and insulin concentrations and insulin resistance
- Gastrointestinal effects, including gastritis, peptic ulceration, and gastrointestinal hemorrhage
- Headache
- Hyper- or hypokalemia; hyper- or hyponatremia
- Hyper- or hypoglycemia; impaired glucose tolerance
- Hyper- or hypotension
- Impaired exercise tolerance
- Infertility
- Ischemic heart disease, subclinical atherosclerosis
- Lower bone mineral density
- Myopathies
- Obesity
- Psychiatric disorders, substance use disorders, mood swings, challenges with social interactions
- Seizures have been reported during episodes of hyponatremia and of hypoglycemia
- Weakness / lethargy / fatigue

8.3 Efficacy Assessments

8.3.1 Hormone Assessments

Blood samples will be collected for measurement of serum 17-OHP and plasma ACTH, testosterone, and androstenedione. Saliva samples will be collected for measurement of 17-OHP.

Background glucocorticoid levels (e.g., cortisol levels if the subject takes hydrocortisone, prednisolone levels if the subject takes prednisone, and dexamethasone levels if the subject takes dexamethasone) will also be measured.

Separate tubes of blood will be collected for serum and plasma, and each sample will be divided into aliquots designated for appropriate assessments and backup. Detailed instructions for the collection and handling of biological samples will be provided separately.

8.4 Pharmacokinetic Assessments

A plasma sample will be collected for measurement of SPR001 concentration at each study visit indicated in the Schedule of Activities.

8.5 Exploratory Assessments

8.5.1 Quality of Life Assessments

QoL will be measured using the SF-36, PGIC, bother score, and CAH signs and symptoms interview, all described in this section. QoL as reflected by mood will be measured using the HADS, which is also used as a measure of safety and is described in Section 8.1.6.2.

8.5.1.1 Short Form 36

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

8.5.1.2 Patient Global Impression of Change

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

8.5.1.3 Bother Score

The bother score is a 1-question survey that asks subjects to evaluate the overall bothersomeness of their CAH symptoms. Subjects select a response on a 7-point scale.

8.5.1.4 Congenital Adrenal Hyperplasia Signs and Symptoms Interview

Subjects will be asked about the following aspects of health relevant to CAH signs and symptoms:

- General health status
- Fatigue

- Activity level
- Concentration
- Sleep
- Appetite
- Mood
- Dizziness
- Sweating
- Fluid retention
- Acne
- Headaches
- Nausea
- Joint/muscle aches
- Back pain
- Weakness
- Moon facies
- Hirsutism

Subjects will be asked to rate on a 5-point scale how frequently they experienced CAH signs and symptoms related to these aspects of health over the last week or since their last clinic visit, whichever is more recent.

8.5.2 Metabolic Assessments

Metabolic assessments that will be conducted as exploratory measures of the effect of SPR001 include fasting glucose, HbA1c, fasting insulin, and lipid panel (described as part of clinical laboratory in Section 12.4) and BW and BMI (described in Section 8.1.3).

8.5.3 Exploratory Adrenal Hormones

A separate blood sample will be drawn at each visit specified in the Schedule of Activities and stored for measurement of exploratory adrenal hormones. Exploratory adrenal hormones may include 11-oxygenated 19-carbon (11oxC19) steroids (11β-hydroxyandrostenedione, 11-ketoandrostenedione, 11β-hydroxytestosterone, and 11-ketotestosterone), androsterone, and etiocholanolone.

8.5.4 Sex-Specific Assessments

Refer to Section 8.1.1 on the physical examination for information about assessments of acne and hirsutism in female subjects.

8.5.4.1 Testicular Adrenal Rest Tumors

TARTs are a common complication of CAH caused by ACTH-driven overstimulation of aberrant adrenal cells within the testes (Olpin and Witt, 2014) and result in pain, discomfort, impaired

spermatogenesis, and infertility (Chihaoui et al, 2016; Claahsen-van der Grinten et al, 2014; Delfino et al, 2012). Complete scrotal ultrasounds will be conducted in male subjects using a real-time scanner to detect and to evaluate the size and number of TARTs. Standard images should be obtained in the longitudinal and transverse planes. Each potential TART lesion will be measured in 3 planes to allow for calculation of TART volume. Detailed instructions for performing the scrotal ultrasound will be provided separately. Scrotal ultrasounds will be read by a central radiologist blinded to the study timepoint at which the ultrasounds were taken.

For SPR001-naïve male subjects, a scrotal ultrasound will be conducted at the initial screening visit. For SPR001-experienced male subjects rolling over from Study SPR001-201, a scrotal ultrasound will be conducted at the initial screening visit only if the subject has not had a prior scrotal ultrasound within 3 months before screening. For all male subjects, if the prior or screening scrotal ultrasound reveals no evidence of TART, the scrotal ultrasound need not be repeated at either Day 1 or Week 12. If the prior or screening scrotal ultrasound does show evidence of TART(s), the scrotal ultrasound will be repeated at Day 1 and Week 12.

8.5.4.2 Semen Analysis

All male subjects should be encouraged (though not required) to provide a semen sample at each visit specified in the Schedule of Activities. Semen will be collected from male subjects to assess sperm count, morphology, and motility.

8.5.4.3 Menstrual Cyclicity

Female subjects will record menstrual information (including start and stop dates of menses and whether the flow was light, moderate, or heavy) in a menstrual diary throughout the 12-week screening period and the 12-week treatment period. A menstrual diary will be handed out at the screening visit and collected at the Day 1 visit, and a second menstrual diary will be handed out at the Day 1 visit and collected at the Week 12 visit. These data will be used to assess the menstrual cyclicity endpoint.

8.5.5 Metabolite Identification

Samples remaining after PD and PK evaluation may be stored and used for metabolite identification studies as deemed appropriate.

9 STATISTICAL CONSIDERATIONS

A detailed description of statistical methods to be applied will be provided in the Statistical Analysis Plan (SAP).

9.1 Sample Size Determination

The total sample size of up to approximately 24 subjects in this study is based on an estimate of the number of subjects who may enroll either after completing Study SPR001-201 or as SPR001-naïve subjects. There is no statistical basis for the total sample size.

The study will attempt to enroll an enriched subpopulation of up to approximately 8 male subjects 18 to 35 years old with TARTs. The sample size for this subpopulation is based on the following: 1) the assumptions that 10% of males with TARTs would experience TART shrinkage in 3 months without study treatment and that at least 50% of males with TARTs would experience TART shrinkage in 3 months with study treatment, 2) a power of 85%, and 3) a 2-sided exact test with a significance level of 0.05 to detect a conservative difference of 40%.

9.2 Populations for Analyses and Missing Data

The Safety Population will consist of all enrolled subjects who received at least 1 dose of study drug in this study and will be the primary analysis population.

The Per Protocol Population will consist of all subjects who received at least 80% of study drug doses planned over the entire treatment period and had no major protocol deviations. Additional criteria for the Per Protocol Population may be specified in the SAP. The Per Protocol Population will be identified prior to database lock.

Conventions for the handling of missing data will be described in the SAP.

9.3 Statistical Analyses

9.3.1 General Approach

Summarized data will represent overall data pooled from all subjects within each analysis population. Changes in primary, secondary, and exploratory endpoints will be analyzed over time, with change from baseline summarized for each post-baseline time point measured. If SPR001 dosing is adjusted for subjects who enroll later on in this study, data will be presented by SPR001 dose. Unless otherwise specified, statistical analysis will be performed using SAS version 9.3 or higher.

9.3.2 Demographics and Baseline Descriptive Statistics

Demographics and subject background information such as disease characteristics will be summarized using descriptive statistics, including the number of subjects (n), mean, standard deviation, median, and range for continuous variables and count and percentage for categorical variables. Medical history will be listed.

9.3.3 Subject Disposition

Subject disposition data such as the numbers of screen failures, enrolled subjects, subjects with dose reductions, subjects who discontinued study drug/withdrew from the study early, and subjects who completed the study will be summarized using descriptive statistics.

9.3.4 Subject Compliance

The planned and actual doses of study drug administered and reason for any dose change will be listed by subject. Study drug compliance will be calculated for each subject and summarized descriptively overall and by SPR001 dose, if applicable.

9.3.5 Safety Analyses

Safety analyses will be performed on the Safety Population.

AEs will be coded using MedDRA Version 20 or higher and presented by System Organ Class and Preferred Term. AEs that occur before the first dose of study drug will be distinguished from TEAEs. TEAEs will be listed by subject and summarized overall and by SPR001 dose, if applicable. The incidence of each TEAE will be tabulated and presented by maximum severity. The frequency (number and percentage) of subjects who experience ≥1 TEAE will be summarized. TEAEs potentially related to study drug, SAEs, AEs leading to study drug discontinuation/study withdrawal, DLTs, and AESIs will be summarized by frequency of subjects who experience ≥1 event and/or tabulated by incidence for each event.

Physical examination findings will be listed. Vital signs, ECG parameters, and clinical laboratory values will be listed and summarized using descriptive statistics. Investigators' assessments of ECG results will be listed and summarized in a frequency table. Clinical laboratory values may be presented in shift tables. Prior and concomitant medications will be listed. C-SSRS data will be listed. Data for the HADS (including anxiety and depression subscales) will be summarized using descriptive statistics.

An SRC will review safety data at regular intervals throughout the study (see Section 10.6).

Additional analyses may be performed if warranted upon review of the data.

9.3.6 Efficacy Analyses

Efficacy analyses will be performed on both the Safety and Per Protocol Populations.

Changes over time in hormones (ACTH, 17-OHP, androstenedione, testosterone, and exploratory adrenal hormones) will be summarized using descriptive statistics and presented in tables and/or graphs. Parametric (paired t test) or nonparametric (Wilcoxon signed rank) tests will be used to test the change from baseline depending on the data distribution.

Data for the SF-36 (including individual domain scores and summary scores) will be summarized using descriptive statistics. Data for the PGIC, the bother score, and the CAH signs and symptoms interview will be summarized using counts and percentages. Shifts in status from baseline to each post-baseline visit will be presented.

Changes over time in metabolic parameters (including fasting glucose, HbA1c, fasting insulin, lipid profile, BW, and BMI) will be summarized using descriptive statistics.

Changes over time in measures of TARTs and on semen analysis in male subjects and in measures of acne, hirsutism, and menstrual cyclicity in female subjects will be summarized using descriptive statistics.

Additional analyses may be performed if warranted upon review of the data.

9.3.7 Pharmacokinetics Analyses

PK may be assessed using a population PK approach. Any population PK analysis will be described in a separate population PK analysis plan.

9.3.8 Planned Interim Analyses

Interim ad-hoc analyses may be performed.

An SRC will review safety data at regular intervals throughout the study (see Section 10.6).

9.3.9 Subgroup Analyses

Descriptive summaries of primary, secondary, and exploratory endpoints will be provided by sex and by subject status as being either SPR001-naïve or SPR001-experienced on entering this study. Any additional subgroup analyses will be specified in the SAP.

9.3.10 Exploratory Analyses

Any exploratory analyses will be specified in the SAP.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Informed Consent

Eligible subjects may only be enrolled into the study after providing written (and witnessed, where required by law or regulation), IRB-approved informed consent. Informed consent must be obtained before conducting any protocol-specified procedures. The process of obtaining informed consent should be documented in the subject source documents.

Any changes to the proposed consent form suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB, and a copy of the approved version must be provided to the Sponsor after IRB approval.

10.2 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 at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of SPR001 at any time.

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

10.3 Confidentiality and Privacy

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

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

10.4 Future Use of Stored Specimens and Data

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

10.5 Key Roles and Study Governance

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

10.6 Safety Oversight

An SRC composed of appropriate medical and clinical representatives will review safety data at regular intervals throughout the study and provide recommendations regarding further enrollment and dosing or any adjustments to dosing to the Sponsor, who will ultimately decide on any changes in this study. A separate charter will detail the responsibilities of the SRC.

10.7 Clinical Monitoring

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

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

Refer to Section 10.9.1 for information on eCRFs and source documents.

10.8 Quality Assurance and Quality Control

Representatives of the Sponsor must be allowed to visit all study site locations periodically to assess the data, quality, and study integrity. Onsite, they will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. In addition, 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. Spruce 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 Spruce.

10.9 Data Handling and Record Keeping

10.9.1 Data Collection and Management Responsibilities

An eCRF must be completed for each enrolled subject. Completed original case report forms are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

It is the Investigator's responsibility to ensure completion of and to review and approve all eCRFs. Case report forms must be signed by the Investigator or by an authorized staff member. These signatures serve to attest that the information contained on the eCRFs is true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRFs.

For each subject in the study, the Investigator must maintain source documents at the trial site consisting of case and visit notes that contain demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. In most cases, the source documents will be the hospital/clinic or physician medical records/chart. 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. The Investigator must also keep the original ICF signed by the subject (a copy of the signed ICF is given to the subject).

10.9.2 Study Records Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor or its designees, the Investigator agrees to keep records that include the identity of all subjects (sufficient information to link records [e.g., 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 or local regulations or the Clinical Study Agreement dictates, whichever is longer.

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

10.10 Protocol Deviations

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

If a protocol deviation is implemented to eliminate an immediate hazard before a protocol amendment can be submitted for IRB review and approval/favorable opinion (see

Section 10.12), 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.

10.11 Publication and Data Sharing Policy

Manuscripts for publication will be prepared in accordance with the Sponsor's publication policy. Manuscripts must be submitted to the Sponsor for review and comment before submission to a publisher. This requirement should not be construed as a means of restricting publication but is intended solely to ensure concurrence regarding data, evaluations, and conclusions and to provide an opportunity for the Sponsor to share with the Investigator any new or unpublished information of which the Investigator may be unaware.

10.12 Amendments

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

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

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

11 REFERENCES

Arlt W, Willis DS, Wild SH, et al. Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. *J Clin Endocrinol Metab.* 2010;95(11):5110-5121.

Auchus RJ. Management considerations for the adult with congenital adrenal hyperplasia. *Mol Cell Endocrinol.* 2015;408:190-197.

Aulinas A, Webb SM. Health-related quality of life in primary and secondary adrenal insufficiency. *Expert Rev Pharmacoecon Outcomes Res*. 2014;14(6):873-888.

Bachelot A, Chakthoura Z, Rouxel A, et al. Classical forms of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults. *Horm Res.* 2008;69:203-211.

Bachelot A, Golmard JL, Dulon J, et al. Determining clinical and biological indicators for health outcomes in adult patients with childhood onset of congenital adrenal hyperplasia. *Eur J Endocrinol.* 2015;173:175-84.

Chihaoui M, Kanoun F, Chaker F, et al. Testicular adrenal rest tumours in young adult males with congenital adrenal hyperplasia: prevalence and impact on testicular function. *Andrologia*. 2016;48(1):45-50.

Choi JH, Kim GH, Yoo HW. Recent advances in biochemical and molecular analysis of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Ann Pediatr Endocrinol Metab.* 2016;21:1-6.

Claahsen-van der Grinten HL, Dehzad F, Kamphuis-van Ulzen K, de Korte CL. Increased prevalence of testicular adrenal rest tumours during adolescence in congenital adrenal hyperplasia. *Horm Res Paediatr*. 2014;82(4):238-244.

Delfino M, Elia J, Imbrogno N, et al. Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia: prevalence and sonographic, hormonal, and seminal characteristics. *J Ultrasound in Med*. 2012;31(3):383-388.

Doleschall M, Szabó JA, Pázmándi J, et al. Common genetic variants of the human steroid 21-hydroxylase gene (CYP21A2) are related to differences in circulating hormone levels. *PLoS One.* 2014;9:e107244.

Falhammar H, Frisén L, Norrby C, et al. Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab.* 2014;99(12):E2715-2721.

Falhammar H, Wedell A, Nordenström A. Biochemical and genetic diagnosis of 21-hydroxylase deficiency. *Endocrine.* 2015;50(2):306-314.

Food and Drug Administration. Guidance for Industry. Acne Vulgaris: Developing Drugs for Treatment. Draft Guidance. September 2005. Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064981.htm

Gilban DL, Alves Jr PA, Beserra IC. Health-related quality of life of children and adolescents with congenital adrenal hyperplasia in Brazil. *Health Qual Life Outcomes*. 2014;12:107.

Guy W (ed). *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.

Han TS, Stimson RH, Rees DA, et al. Glucocorticoid treatment regimen and health outcomes in adults with congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)*. 2013;78(2):197-203.

Han TS, Walker BR, Arlt W, et al. Treatment and health outcomes in adults with congenital adrenal hyperplasia. *Nat Rev Endocrinol.* 2014;10:115-124.

Hummel SR, Sadler S, Whitaker MJ, Ara RM, Dixon S, Ross RJ. A model for measuring the health burden of classic congenital adrenal hyperplasia in adults. *Clin Endocrinol (Oxf*). 2016;85(3):361-398.

Martin KA, Anderson RR, Chang RJ, et al. Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(4):1-25.

Mnif MF, Kamoun M, Mnif F, et al. Long-term outcome of patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Am J Med Sci*. 2012;344:363-73.

Olpin JD and Witt B. Testicular adrenal rest tumors in a patient with congenital adrenal hyperplasia. *J Radiol Case Rep*. 2014;8(2):46-53.

Reisch N. Substitution therapy in adult patients with congenital adrenal hyperplasia. *Best Pract Res Clin Endocrinol Metab.* 2015;29:33-45.

Turcu AF, Auchus RJ. Adrenal steroidogenesis and congenital adrenal hyperplasia. *Endocrinol Metab Clin North Am.* 2015;44(2):275-296.

Turcu AF, Spencer-Segal JL, Farber RH, et al. Single-Dose study of a corticotropin-releasing factor receptor-1 antagonist in women with 21-hydroxylase deficiency. *J Clin Endocrinol Metab.* 2016;101(3):1174-1180.

Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). *Med Care*. 1992;30(6):473-483.

White PC and Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev*. 2000;21:245-291.

Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. *Human Reprod Update*. 2010;16(1);51-64.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;*67*(6):361-370.

12 APPENDICES

12.1 Appendix of Prohibited Concomitant Medications and Concomitant Medications of Concern

12.1.1 List of Prohibited Concomitant Medications

Other investigational drugs are prohibited during the study.

Rosiglitazone treatment is prohibited during the study because it could affect the subject's ACTH levels. Treatment with testosterone is also prohibited. In general, subjects who require ongoing treatment with rosiglitazone or testosterone should not be screened.

Potent inducers or inhibitors of CYP3A4 are generally prohibited because of their potential impact on the metabolism of SPR001. Stable daily doses of glucocorticoids and birth control are not restricted. The following CYP3A4 inducers and inhibitors are specifically prohibited:

Butalbital	Phenobarbital
Carbamazepine	Phenytoin
Chloramphenicol	Pioglitazone
Clarithromycin	Posaconazole
Conivaptan	Quercetin
Itraconazole	Rifabutin
Ketoconazole	Rifampin
Mibefradil	St. John's Wort
Modafinil	Telithromycin
Nefazodone	Topiramate
Oxcarbazepine	Voriconazole

Many medications used to treat HCV and HIV are strong inhibitors of CYP3A4 but are not listed here because patients with HIV and/or HCV are excluded from this study.

12.1.2 List of Concomitant Medications of Concern

The following drugs metabolized by CYP3A4, 2C8, 2C9, and/or 2C19 are sensitive substrates of these enzymes or substrates with narrow therapeutic windows and should be avoided as much as possible:

Alfentanil	Lovastatin
Aprepitant	Lurasidone
Avanafil	Midazolam
Budesonide	Nalogexol
Buspirone	Nisoldipine
Capsaicin	Omeprazole
Celecoxib	Pimozide
Clobazam	Quetiapine
Darifenacin	Quinidine
Dihydroergotamine	Repaglanide
Dronedarone	Sildenafil
Eletriptan	Simvastatin
Eplerenone	Tacrolimus
Ergotamine	Ticagrelor
Felodipine	Tolvaptan
Fentanyl	Triazolam
Fluticasone	Vardenafil
Lansoprazole	Warfarin
Lomitapide	

12.2 Appendix of Liver Safety

12.2.1 Liver Chemistry Stopping Criteria and Follow-up Assessments

Liver Chemistry Stopping Criteria	
Absolute ALT	ALT ≥5x ULN
Increase in ALT	ALT ≥3x ULN persists for ≥4 weeks
Bilirubin[1,2]	ALT ≥3x ULN **and** bilirubin ≥2x ULN (>35% direct bilirubin)
INR[2]	ALT ≥3x ULN **and** INR >1.5, if INR measured
Cannot Monitor	ALT ≥3x ULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥3x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions and Follow-up Assessments	
Actions	**Follow-up Assessments**
• Immediately discontinue study drug. • Report the event to the Sponsor or designated CRO within 24 hours. • Complete the liver event eCRF, and complete an SAE data collection tool if the event also met the criteria for an SAE.[2] • Request list of any medications taken in last 48 hours; specifically question about medications that are known to increase liver enzymes, such as aspirin, acetaminophen, ibuprofen, naproxen, diclofenac, phenylbutazone, and any antibiotic use. • Perform liver chemistry follow-up assessments. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see MONITORING below). • If restart/rechallenge is not granted, permanently discontinue study drug and continue participant in the study for any protocol-specified follow-up assessments. **MONITORING:** **<u>If ALT ≥3x ULN AND bilirubin ≥2x ULN or INR >1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, and bilirubin) and perform liver event follow-up assessments within **24 hours**.	• Viral hepatitis serology.[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminase values show downward trend. • Obtain blood sample for PK analysis after the most recent dose.[5] • Serum CPK and LDH. • Fractionate bilirubin, if total bilirubin ≥2x ULN. • Obtain complete blood count with differential to assess eosinophilia. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form. • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event eCRF. **<u>If ALT ≥3x ULN AND bilirubin ≥2x ULN or INR >1.5:</u>** • Anti-nuclear antibody, anti–smooth muscle antibody, type 1 anti-liver kidney microsomal

• Monitor subject twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **<u>If ALT ≥3x ULN AND bilirubin <2x ULN and INR ≤1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within 24 to 72 hours. • Monitor subjects weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury) in subjects with definite or likely acetaminophen use in the preceding week. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate transaminase; CPK = creatine phosphokinase; CRO = contract research organization; HPLC = high-performance liquid chromatography; IgG = immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal.

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

[2] All events of ALT ≥3x ULN and bilirubin ≥2x ULN (>35% direct bilirubin) or ALT ≥3x ULN and INR >1.5 may indicate severe liver injury (possible "Hy's Law") and must be reported as an SAE.

[3] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).

[4] Includes hepatitis A IgM antibody, hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb), hepatitis C RNA, cytomegalovirus IgM antibody, Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing), and hepatitis E IgM antibody.

[5] Record the date/time of the PK blood sample draw and the date/time of the last dose of study drug before the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping will be provided in the laboratory manual from the applicable central laboratory.

12.2.2 Criterion for Increased Liver Chemistry Monitoring While Continuing Study Drug

Criterion for Increased Liver Chemistry Monitoring and Follow-up Actions	
Criterion	**Actions**
ALT ≥3x ULN and <5x ULN **and** bilirubin <2x ULN, **without** symptoms believed to be related to liver injury or hypersensitivity, **and** can be monitored weekly for 4 weeks	• Notify the Medical Monitor within **24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study drug. • Subject must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) until the abnormalities resolve, stabilize, or return to baseline. • If at any time the subject meets liver chemistry stopping criteria, proceed as described in Section 7.2.1 and Section 12.2.1.

	• If, after 4 weeks of monitoring, ALT <3x ULN and bilirubin <2x ULN, monitor per standard scheduling for remainder of study and follow-up period.

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

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

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

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

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

12.3 Appendix of Potentially Clinically Significant Adverse Events

12.3.1 List of Potentially Clinically Significant Signs and Symptoms

Event	Description
Abdominal Pain	Pain and abdominal tenderness to palpation that significantly impairs ambulation, food intake, and ADL for >24 hours
Nausea/Vomiting	>3 episodes of emesis over >4 continuous hours with continuous nausea
Diarrhea	>3 episodes of unformed stools and fecal urgency over >8 hours
Dizziness/Hypotension	Orthostatic CNS symptoms (dizziness, confusion) that prevent ambulation for >3 hours, associated with orthostatic SBP decrease >20 mmHg or DBP decrease >10 mmHg or upright heart rate >105 bpm, and are not vasovagal responses to provocative stimuli (e.g., phlebotomy, nausea, bowel or bladder function)
Sensorium	Disorientation to time, place, or identity. Any abnormal ideation.
Mood	Feelings of grief or loss that interfere with study procedures. Any suicidal ideation.
Headache/Pain	Any focal or generalized head pain that disrupts normal activities over >12 hours and is not responsive to 2 doses of non-steroidal analgesics
Pruritis	Generalized itching over >24 hours unresponsive to oral antihistamine
Systolic Blood Pressure	>30 mmHg increase from baseline values or an absolute level >180 mmHg
Diastolic Blood Pressure	>20 mmHg increase from baseline values or an absolute level >110 mmHg
Heart Rate	Resting (sitting or recumbent) HR >110 bpm
Cardiac Rhythm	Any rhythm other than sinus rhythm, sinus bradycardia, or mild sinus tachycardia
QRS Morphology	Significant prolongation of QRS interval or new onset of bundle branch block
Skin Rash	Pruritic rash or urticaria over >100 cm^2 in area in more than one location simultaneously
Neurological Signs	New onset of readily visible tremor during normal movement, clonic reflexes, or motor dyscoordination, convulsions, or seizures

Abbreviations: ADL, activities of daily living; bpm, beats per minute; CNS, central nervous system; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

12.3.2 List of Potentially Clinically Significant Laboratory Findings

Lab	Criteria
Hemoglobin	>2 g/dL reduction from baseline or absolute value <10 g/dL
Neutropenia	Absolute neutrophil count <1,800/µL and >500/µL reduction from baseline
Lymphopenia	Absolute lymphocyte count <500/µL
Platelet count	<50,000/µL

Lab	Criteria
Creatinine	>1.8 mg/dL or >0.4 mg/dL increase from baseline value
BUN	>30 mg/dL and >10 mg/dL increase from baseline values
ALT	>3-fold above laboratory reference upper limit value
AST	>3-fold above laboratory reference upper limit value
Bilirubin (total)	>1.5-fold above laboratory reference upper limit value
Potassium	<3.0 or >5.5 meq/L
Sodium	<130 or >150 meq/L
Serum calcium	>11.4 mg/dL sustained over 24 hours
FSH	>15 if baseline value was <5

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FSH, follicle-stimulating hormone.

Note: If a laboratory result meets any of these criteria, it should be confirmed by repeat measurement within 48 hours.

12.4 Appendix of Clinical Laboratory Tests

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

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

[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 12.2. All events of ALT ≥3x ULN plus bilirubin ≥2x ULN (>35% direct bilirubin) or ALT ≥3x ULN plus INR >1.5 (if INR is measured) may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.