CLINICAL STUDY PROTOCOL

A Phase 2, Multiple-Dose, Dose-Escalation Study to Evaluate the Safety and Efficacy of SPR001 in Adults with Classic Congenital Adrenal Hyperplasia (CAH)

Study Number:	SPR001-201
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INVESTIGATOR PROTOCOL AGREEMENT

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations, as well as the "Guideline for Good Clinical Practice," International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). *

The signature below constitutes that I agree to the following:

- That I have reviewed the protocol and the attachments.
- That this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable local and federal regulations and ICH guidelines.
- Not to implement any changes to, or deviations from the protocol without prior agreement from Spruce Biosciences and documented approval from the Institutional Review Board (IRB), except to eliminate an immediate hazard to the subjects or when change(s) involves only logistical or administrative aspects of the study.
- To permit periodic site monitoring of case report forms and source documents by Spruce Biosciences or designee and by appropriate regulatory authorities.
- 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.
- I agree to supply Spruce Biosciences with any information regarding ownership interest and financial ties with the Sponsor for the purpose of complying with regulatory requirements.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

*In accordance with the most recent version of the Declaration of Helsinki.

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Protocol No.	SPR001-201
Study Phase	2
Study Title	A Phase 2, Multiple-Dose, Dose-Escalation Study to Evaluate the Safety and Efficacy of SPR001 in Adults with Classic Congenital Adrenal Hyperplasia (CAH)
Purpose	CAH is a deficiency of critical enzymatic activity within the steroidogenic pathways that lead to the biosynthesis of cortisol. CAH is chronically debilitating because of the development of adrenal insufficiency, precocious puberty, impaired growth, virilization in females, hirsutism, seborrhea, amenorrhea, irregular menses, impaired fertility, testicular adrenal rest tumors (TART), fatigue, anxiety, depression, hyponatremia, hyperkalemia, dehydration, and hypotension, all of which can occur even in the context of routine glucocorticoid (± mineralocorticoid) replacement. In extreme situations, CAH can be life threatening. Patients with CAH whose symptoms are not adequately controlled with physiological glucocorticoid replacement require additional therapy to control androgen excess and mitigate the requirement for glucocorticoid over-replacement, which leads to symptoms of iatrogenic Cushing's Disease. Since elevated adrenocorticotropin hormone (ACTH) is the primary driver for adrenal steroid production in patients with CAH, blocking ACTH synthesis using SPR001, a small-molecule antagonist of the corticotropin-releasing factor type-1 (CRF_1) receptor, may reduce adrenal steroid production while obviating the need for supraphysiologic doses of glucocorticoids. This mechanism of action has been validated in a proof-of-concept study blocking CRF_1 receptors through the use of a similar small-molecule CRF_1 receptor antagonist, which demonstrated a dose-dependent reduction in ACTH and 17-hydroxyprogesterone (17-OHP) in patients with CAH. These promising results provide a rationale for investigating the use of SPR001, a small-molecule CRF_1 receptor antagonist with high affinity and selectivity, combined with replacement glucocorticoids and mineralocorticoids, for the treatment of classic CAH.
Objectives	**Primary** • To evaluate the safety of SPR001 in subjects with CAH • To assess the efficacy of SPR001 in subjects with classic CAH as measured by percent and absolute change in 17-OHP compared to baseline **Secondary** • To explore the dose(s) of SPR001 that cause pharmacodynamic (PD) changes in plasma concentrations of ACTH, androstenedione, and testosterone, as measured by the absolute and percent change from baseline by dose • To determine pharmacokinetics (PK) of SPR001 in subjects with CAH • To explore potential relationships between PK and PD **Exploratory** • To explore the dose(s) of SPR001 that cause changes in PD biomarkers in urine, as measured by the absolute and percent change from baseline by dose

Number of Subjects and Centers	Up to approximately 12 centers in the United States will participate. Cohort A will enroll approximately 9 subjects. Cohorts B, C, and D are part of an adaptive multiple-ascending-dose (MAD) design and will each enroll at least 3 subjects and in general no more than 6 subjects. However, a maximum of 12 subjects may be treated at any single dose level of SPR001 under this protocol (see study design below).

Inclusion/Exclusion Criteria	**Inclusion Criteria**
	
	• Male and female subjects age 18 or older.
	• Documented historical diagnosis of classic CAH due to 21-hydroxylase deficiency based on documented genetic mutation in the CYP21A2 enzyme consistent with a diagnosis of classic CAH or historical documentation of elevated 17-OHP.
	• On a stable regimen of glucocorticoid replacement for a minimum of 30 days before baseline that is expected to remain stable throughout the study.
	  o In Cohort A only, to standardize glucocorticoid replacement regimens and mitigate any potential for drug-drug interactions with SPR001, subjects who currently take any of their glucocorticoid doses after 6p (ie, at bedtime) will be required to take their evening glucocorticoid dose no later than 6p each day for at least 14 days before baseline.
	• Elevated adrenal androgens, defined as 17-OHP ≥800 ng/dL.
	• Male participants must agree to follow contraception guidelines (Section 12.5 [Appendix 5]) and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study medication.
	• Female participants of childbearing potential must agree to follow appropriate contraception guidelines (Section 12.5 [Appendix 5]).
	• Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all aspects of the trial.
	
	Exclusion Criteria
	
	• Clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
	  o A malignancy or less than 3 years of remission history from any malignancy, other than successfully treated localized skin cancer.
	  o Presence of clinically significant renal disease, as evidenced by an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2.
	  o Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
	  o Confirmed positive test at screening for active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).
	• Clinically significant psychiatric disorders either by history or from the Mini International Neuropsychiatric Interview (M.I.N.I.) conducted at Screening, yielding 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.
	• Beck Depression Inventory-II (BDI-II) score >29. For BDI-II scores >29 at screening, the site should discuss with the Medical Monitor to determine if the subject is eligible for this study.
	• At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at Screening

	and Baseline (eg, C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months). • 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: o Clinically meaningful abnormal electrocardiogram (ECG) results, in the opinion of the Investigator. o Fridericia-corrected QT interval (QTcF) >450 msec for male participants or QTcF >470 msec for female participants. o Alanine aminotransferase (ALT) >2x upper limit of normal (ULN). o Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). • Known or suspected differential diagnosis of any of the other known forms of CAH, including non-classic CAH, requires Medical Monitor approval prior to enrollment. • A history that includes bilateral adrenalectomy or hypopituitarism. • Subjects who routinely work overnight shifts require Medical Monitor approval prior to enrollment. • Pregnant or nursing females. • Use of any other investigational drug within 30 days or 5 half-lives (whichever is longer) before initial screening. • As outlined in Section 12.8 (Appendix 8), required use of prohibited concomitant medications, including rosiglitazone 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 first dose of study drug. Those medications identified in Section 12.8 (Appendix 8) as sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine if 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) prior to first dose of study drug. • Unable to understand and comply with the study procedures, unable to understand the risks involved, and/or unwilling to provide written informed consent. • Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.
Study Design	**<u>Cohort A</u>** Cohort A is a 6-week, multiple-dose, intra-subject dose-escalation study of SPR001 in approximately 9 adults with CAH. Subjects in Cohort A will undergo dose escalation through 3 dose levels of SPR001, beginning with 200 mg/day for 2 weeks, then escalating to 600 mg/day for 2 weeks, then escalating to 1000 mg/day for 2 weeks. If a subject develops dose-limiting toxicity (DLT), the subject's dose may be reduced according to Section 8.1. During the treatment period, SPR001 will be administered as an oral daily dose at 10p (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack. The 6-week treatment period will be followed by a 30-day washout and safety follow-up period. The Schedule of Assessments for Cohort A is provided in Section 2.1. Subjects will have a total of 5 overnight visits for PK/PD profiling, with serial blood samples collected over the course of 10 hours during each overnight visit. The 5 overnight visits will consist of a baseline overnight hormone profile 1 day before the first dose of study drug, an overnight profile with the first dose of study drug, and overnight profiles at Day 14 (steady state) of

	each dose period. Subjects will have a final follow-up outpatient visit 30 days after the last dose of study drug. Based on review of the available safety, PK, and PD data from Cohort A and the recommendations of the safety review committee (SRC), an adaptive MAD sequence of 3 cohorts is planned after completion of enrollment in Cohort A. **Cohorts B/C/D** An adaptive MAD design with 3 sequential cohorts (Cohorts B, C, and D) is planned to evaluate the safety, PK, and PD of various SPR001 dosing regimens and to identify an optimal dose regimen. Each cohort will undergo a 2-week run-in period, a 2-week treatment period, and a 30-day washout and safety follow-up period. During the run-in period, which will occur during screening, subjects will document in a paper diary each dose of glucocorticoid medication taken, the time of each meal, and the time they went to bed and woke up each day, to ensure compliance with background glucocorticoid regimens and the stability of their daily routine. Each cohort will initially enroll 3 subjects and may later enroll 3 more subjects based on interim data from the first 3 subjects, for a total of 6 subjects per cohort. However, if safety, PK, and PD results from 6 subjects are inconclusive, a cohort may be expanded up to a maximum of 12 subjects. Cohort B will receive study drug at 200 mg twice daily (BID). Cohort C will receive study drug at 100 mg BID. For BID regimens, subjects will take a dose at 10a and a dose at 10p, either with a meal or 5 to 15 minutes after consumption of a standardized snack. For Cohort D, the dose level and the frequency and timing of dosing will be determined based on interim data from the previous cohorts. However, the dose level of Cohort D will be capped at 800 mg/day. Additionally, the steady-state exposure will be estimated for each dose cohort before initiating higher dose cohorts to ensure that the area under the concentration-time curve (AUC) over a 24-hour interval does not exceed a maximum of 100,000 ng·h/mL. Thus, dosing in this study will not exceed ***either*** a maximum dose of 800 mg/day ***or*** a maximum 24-hour AUC of 100,000 ng·h/mL, whichever limit is equivalent to a lower dose. Decisions regarding continuation or suspension of dosing, cohort expansion, and the dose level and timing of doses for the next cohort will be made by the Sponsor after the SRC reviews interim safety, PK, and PD data and provides its recommendations. Interim data will be analyzed for the first 3 subjects in each cohort after each subject completes the 2 weeks of SPR001 dosing and on an ongoing basis. In particular, the occurrence of any clinically significant adverse event (AE) will receive special consideration and will be reported to the SRC within 1 day of awareness for immediate review. Clinically significant AEs include but are not limited to DLTs, serious adverse events (SAEs), AEs leading to study drug discontinuation, and AEs of special interest (Section 9.3.4), all considered at least possibly related to study drug. Based on recommendations from the SRC and the safety, tolerability, and PK/PD profile of SPR001, the Sponsor may implement any of the following actions: • If ≤1 subject among the first 3 subjects of a cohort experiences a clinically significant AE, the Sponsor may elect to continue with enrollment of an additional 3 subjects into that cohort. If ≤1 subject among the 6 subjects of a cohort experiences a clinically significant AE, the Sponsor may then elect to proceed with enrollment of the next cohort. • If exactly 2 subjects among the first 3 subjects in a cohort experience a clinically significant AE, the Sponsor will suspend dosing in that cohort, and the SRC will make recommendations on next steps. • If exactly 2 subjects among the 6 subjects of a cohort experience a clinically significant AE, the Sponsor may elect to enroll an additional 3 subjects into that cohort at the same dose. If no additional clinically significant AEs occur, the

	Sponsor may then elect to proceed with enrollment of the next cohort. • If ≥3 subjects in a dose cohort experience a clinically significant AE, the Sponsor will suspend dosing and enrollment in that cohort and/or any further dose escalation in the study. Additional subjects may be enrolled at the previous or an intermediate dose. • If data from the first 3 subjects in a cohort indicate suboptimal drug exposure and efficacy (based on PK and PD biomarkers after 2 weeks of SPR001 dosing) and there are no significant safety issues such as clinically significant AEs, the Sponsor may elect to discontinue further enrollment in that cohort and proceed directly to the next cohort. • If safety, PK, and PD data from 6 subjects in a cohort are inconclusive, the Sponsor may elect to increase enrollment of a cohort and/or repeat a cohort, up to a maximum of 12 subjects treated at a single dose level of SPR001 under this protocol. Additionally, the Sponsor may elect to modify the timing of SPR001 dosing to enhance PD effects on CAH biomarkers of interest. The Sponsor may also elect to modify existing glucocorticoid regimens in order to (1) better isolate the PD effects of SPR001 on CAH by minimizing any confounding effects of existing background therapies and/or (2) evaluate for any potential drug-drug interactions between SPR001 and existing glucocorticoid regimens. The Schedule of Assessments for Cohorts B/C/D is provided in Section 2.2. Subjects will have 2 inpatient visits, one for baseline PD profiling after the 2-week run-in period and before starting study drug and one for both PK and PD profiling after 2 weeks on study drug. Serial blood samples will be collected over the course of 24 hours during each inpatient visit. Subjects will also have a pre-dose morning outpatient visit at Day 8 and a follow-up outpatient visit 30 days after the last dose of study drug. Subjects will be assigned to cohorts on the basis of their order of entry into the study. A subject may enroll in >1 cohort if the subject experienced no clinically significant AE in the previous cohort and the Sponsor provides approval. For subjects who do participate in >1 cohort, the final safety follow-up visit of the subject's previous cohort (which occurs after a 30-day washout of study drug) may serve as the screening visit of the subject's next cohort.
Investigational Drug	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. Study drug capsules will be packaged in a high-density polyethylene (HDPE) bottle with a child-resistant cap and an induction foil seal. Capsules containing 50 mg drug substance are size 4 and packaged with 32 capsules per bottle in a 30-mL bottle with a 28-mm cap. Capsules containing 200 mg drug substance are size 1 and packaged either with 14 capsules per bottle (in a 30-mL bottle with a 28-mm cap) or with 60 capsules per bottle (in a 75-mL bottle with a 33-mm cap). Medication labels will comply with legal requirements and will be printed in English. They will supply no information about the subject. The storage conditions (room temperature) will be described on the medication label. Dosing directions will be provided by the site.
Duration of Study	**Cohort A** The expected study duration for each subject in Cohort A will be 10 to 14 weeks. This includes 1 to 30 days for screening, 6 weeks for dosing, and 4 weeks for washout and safety follow-up.

	Cohorts B/C/D The expected study duration for each subject in Cohorts B/C/D will be 8 to 12 weeks. This includes 14 to 45 days for screening (including a 2-week run-in period), 2 weeks for dosing, and 30 days for washout and safety follow-up.
Safety Assessments	Safety will be assessed on an ongoing basis by monitoring for AEs, including identifying any DLTs; physical examinations and vital signs; changes in clinical laboratory values; and changes in BDI-II, C-SSRS, and HADS results. A DLT is defined as a ≥Grade 3 AE (CTCAE version 4.03) that is considered at least possibly related to study drug. A clinically significant AE includes but is not limited to any DLT, SAE, AE leading to study drug discontinuation, or AE of special interest (see Section 9.3.4), all considered at least possibly related to study drug. An SRC composed of appropriate medical and clinical representatives will review safety data at regular intervals throughout the study and make recommendations regarding further cohort enrollment, dose escalation, and dose selection. A separate charter will detail the responsibilities of the SRC.
Efficacy Assessments	**Primary efficacy parameter** • Serum concentration of 17-OHP as measured by the change from baseline, by dose and time. **Secondary efficacy parameters** • ACTH, androstenedione, and testosterone as measured by the change from baseline values, by dose and time. • Changes in patient-reported outcomes measured using the CAH signs and symptoms interview, the Short Form 36 (SF-36), and the Patient Global Impression of Change (PGIC). **Exploratory efficacy parameters** • PD biomarkers in urine as measured by the change from baseline by dose
Pharmacokinetics and Pharmacodynamics	In Cohort A, serial blood samples will be drawn for baseline PD measurements only during the overnight visit that starts on Day -1 and for both PK/PD measurements during the overnight visits that start on Days 0, 13, 27, and 41. The first timepoint for serial blood sampling will be immediately pre-dose (or, for baseline PD, at 10p on Day -1). Subsequent timepoints will be at 4, 5, 6, 8, and 10 hours thereafter. In Cohorts B/C/D, serial blood samples will be drawn for baseline PD measurements only at the baseline visit and for both PK/PD measurements at the end of the 2-week treatment period. The first timepoint for serial blood sampling will be immediately before the AM dose (or, for baseline PD, at the time the AM dose of study drug would be). Subsequent timepoints will be at 2, 3, 4, 5, 6, 7, and 8 hours after the time corresponding to the AM dose, then every 2 hours thereafter through the time corresponding to the PM dose, and at 4, 5, 6, and 8 hours after the time corresponding to the PM dose, then every 2 hours thereafter through the time corresponding to the next AM dose. Thus, for Cohorts B and C, in which study drug will be administered at 10a and 10p, serial blood samples will be drawn at 10a (or immediately pre-dose), 12p, 1p, 2p, 3p, 4p, 5p, 6p, 8p, 10p (or immediately pre-dose), 2a, 3a, 4a, 6a, 8a, and 10a (or immediately pre-dose). A single blood sample will also be drawn for PK/PD measurements at approximately 10a during the Day 8 and safety follow-up outpatient visits. In Cohort D, the number of blood samples for PK/PD measurements will not be increased, but their timing may be adjusted based on changes to the dosing regimen and available PK/PD data from prior cohorts. In Cohorts B/C/D, 24-hour urine samples will be collected during each inpatient visit in

	2 aliquots: the first aliquot from the time corresponding to the AM dose to immediately before the time corresponding to the PM dose, the second aliquot from the time corresponding to the PM dose to immediately before the time corresponding to the subsequent AM dose. Thus, for Cohorts B and C, in which study drug will be administered at 10a and 10p, the first aliquot of 24-hour urine will be collected from 10a to 10p, and the second aliquot will be collected from 10p to 10a the next morning. Urine 17-OHP and free cortisol will be measured. Urine concentrations of SPR001 and exploratory urine biomarkers may also be measured. **Pharmacokinetics** Maximum drug concentration (C_{max}), time of maximum drug concentration (T_{max}), half life ($T_{1/2}$), and AUC will be evaluated for each set of serial plasma samples associated with a dose of SPR001. **Pharmacodynamics** • Descriptive statistics and graphical depiction for SPR001 plasma concentration over time will be provided. • Relationship between SPR001 PK concentration and PD markers of efficacy and safety (eg, 17-OHP, ACTH, androstenedione, testosterone, cortisol, and glucocorticoids) will also be explored. Procedures for sample drawing, handling, storage, and transportation will be provided in the laboratory manual.
Statistical Methods and Data Analysis	**Efficacy and PK/PD Analyses** Demographic and background information will be summarized and presented as descriptive statistics, including standard deviations, medians, and ranges for continuous variables and counts and percentages for categorical variables. PK parameter estimates for SPR001 will be calculated by a standard noncompartmental method of analysis and, where appropriate, by compartmental method of analysis. The primary parameter for analysis will be AUC. An assessment of the dose proportionality and accumulation of SPR001 observed in this study will be conducted. The responses of PD biomarkers to SPR001 will be explored by SPR001 exposure, dose level, and treatment duration. Inferences will be sought regarding the ability of SPR001 to attenuate the early-morning rise in 17-OHP and ACTH and to attenuate accumulation of androstenedione, and testosterone. The effects of SPR001 on PD measures will be explored over a range of doses. Data for the SF-36 (individual domain scores and summary scores) and HADS (anxiety subscale and depression subscale) will be summarized using descriptive statistics and presented by SPR001 dose level and time point. Data for the CAH signs and symptoms interview and PGIC will be summarized using counts and percentages for each SPR001 dose level. **Safety Analyses** Frequencies (number and percentage) of subjects with ≥1 treatment-emergent adverse events (TEAEs) will be summarized by dose group and by System Organ Class and Preferred Term according to Medical Dictionary for Regulatory Activities (MedDRA™) terminology. All TEAEs potentially related to study drug and all SAEs potentially related to study drug will be summarized. The incidence of AEs, their severity, and the incidence of subjects who withdraw due to an AE will be tabulated. Subject listings of all TEAEs and of AEs causing study

	discontinuation will be presented. **Sample Size** A total of 9 subjects will be enrolled into Cohort A. Approximately 3 to 6 subjects are expected to be enrolled into each of Cohorts B, C, and D, for a total of 9 to 18 additional subjects. This sample size is anticipated to provide sufficient data for PK analysis and an estimate of safety and efficacy based on previously conducted Phase 1 studies while maintaining feasible subject recruitment goals for this rare disease.

2 SCHEDULES OF ASSESSMENTS

2.1 Schedule of Assessments for Cohort A

	Screen Phase	First Dosing Period[1]		Ascending-Dose Period[2]			Follow-up/ ET[3]
		Baseline	Dose 1				
Visit No.	**1**	**2a**	**2b**	**3**	**4**	**5**	**6**
Study Day[4]	**-30 to -1**	**(-1) to 0 (overnight)**	**0 to 1 (overnight)**	**13 to 14 (overnight)**	**27 to 28 (overnight)**	**41 to 42 (overnight)**	**Last dose + 30 days**
Informed consent	X						
Inclusion and exclusion criteria	X	X					
Demography	X						
Medical history	X						
Signs and symptoms interview	X	X	X	X	X	X	X
Prior medications from past year	X						
Concomitant medications[5]	X	X	X	X	X	X	X

[1] The first inpatient visit (Visit 2a, baseline) consists of an overnight assessment of subjects' baseline hormonal status (10p of Day -1 to 8a of Day 0). Subjects may leave the site the morning after the first overnight stay and return that same evening for the second overnight stay. The second overnight inpatient visit (Visit 2b, Dose 1) begins the evening of Day 0 and goes through the following morning (Day 1) for a full PK/PD assessment and safety monitoring following the first dose. If no safety issues are noted during the period of observation, subjects will leave with a 2-week supply of SPR001. Sufficient medication will be provided at each visit to allow for loss and/or visit deviations.

[2] During these overnight stays, subjects will take their final dose at their current dose level at 10p in order to obtain steady-state serial PK/PD assessments. On the following day, they will be sent home with sufficient supplies and directions to begin their new dose level that next evening.

[3] The early termination visit should preferably be performed in the morning in order to accommodate the 8a collection of abbreviated PK/PD assessments, androstenedione, testosterone, and salivary 17-OHP.

[4] All visits should be performed on the indicated study days. In cases where this is not possible, the following visit windows apply: ±2 days for Visits 3 to 5, ±7 days for the safety follow-up visit (Visit 6).

[5] Subjects should be on a stable regimen of glucocorticoid replacement, with all glucocorticoid dosing occuring before 6p each day for a minimum of 14 days before baseline and throughout the treatment period. On mornings of study visits with 8a laboratory assessments, subjects should take their morning glucocorticoid replacement after the laboratory assessments.

	Screen Phase	First Dosing Period[1]		Ascending-Dose Period[2]			Follow-up/ ET[3]
		Baseline	Dose 1				
Visit No.	**1**	**2a**	**2b**	**3**	**4**	**5**	**6**
Study Day[4]	**-30 to -1**	**(-1) to 0 (overnight)**	**0 to 1 (overnight)**	**13 to 14 (overnight)**	**27 to 28 (overnight)**	**41 to 42 (overnight)**	**Last dose + 30 days**
Vital signs and body weight	X	X	X[6]	X	X	X	X
Physical examination[7]	X	X	X[6]	X	X	X	X
12-lead ECG	X	X		X	X	X	X
Testicular ultrasound for males	X					X	
M.I.N.I. Version 7.0.2	X						
BDI-II	X	X		X	X	X	X
C-SSRS	X	X		X	X	X	X
Clinical laboratory assessments[8]	X	X		X	X	X	X
Serum 17-OHP (single collection)	X						
Hepatitis B & C and HIV screening	X						
Pregnancy test (WOCBP only)[9]	X	X		X	X	X	X
Genetic sample[10]		X					
Dispense study drug			X	X	X		

[6] At Visit 2b, vital signs assessment and the physical examination should be conducted on the morning of Day 1, after the 8a laboratory assessments and before discharge.
[7] A full physical examination will be conducted at Visit 1 (Screening), Visit 2a (baseline), and Visit 5 (last overnight stay). An abbreviated physical examination will be conducted at Visits 2b, 3, 4, and 6. Height only needs be collected at Screening (Visit 1). Male subjects should have a testicular exam as part of the physical examination at Visit 2a and Visit 5. Female breast and genitalia examinations are not required.
[8] Clinical lab assessments are to be conducted when the subject first arrives at the clinic, prior to the overnight stay (where applicable). Includes serum chemistry, complete blood count, urinalysis, plasma renin, aldosterone, prolactin, progesterone, luteinizing hormone, follicle-stimulating hormone, sex hormone–binding globulin, inhibin B, T3, T4, thyroid-stimulating hormone, estradiol (females).
[9] Serum pregnancy test at screening; in-clinic urine pregnancy test at subsequent visits specified.
[10] Genetic testing is optional for those with previous genetic testing and/or for those who have agreed to participate in the genetic sub-study (separate consent required).

	Screen Phase	First Dosing Period[1]		Ascending-Dose Period[2]			Follow-up/ ET[3]
		Baseline	Dose 1				
Visit No.	**1**	**2a**	**2b**	**3**	**4**	**5**	**6**
Study Day[4]	**-30 to -1**	**(-1) to 0 (overnight)**	**0 to 1 (overnight)**	**13 to 14 (overnight)**	**27 to 28 (overnight)**	**41 to 42 (overnight)**	**Last dose + 30 days**
AE review		X	X	X	X	X	X
Overnight PK/PD (SPR001, 17-OHP, ACTH, cortisol): pre-dose, 4, 5, 6, 8, 10 h post-dose		X[1]	X	X	X	X	
Abbreviated PK/PD assessments (SPR001, 17-OHP, ACTH, cortisol), androstenedione, testosterone – 8a							X[3]
Androstenedione, testosterone – 6a, 8a		X	X	X	X	X	
Salivary 17-OHP – 8a		X	X	X	X	X	X[3]
Phone visit, safety check[11]			1 week post-visit	1 week post-visit	1 week post-visit		

Abbreviations: 17-OHP = 17-hydroxyprogesterone; ACTH = adrenocorticotropin hormone; AE = adverse event; BDI-II = Beck Depression Inventory-II; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; MINI = Mini International Neuropsychiatric Interview; PD = pharmacodynamics; PK = pharmacokinetics; WOCBP = women of childbearing potential.

[11] A call to the subject to assess changes in concomitant medication, study drug compliance based on subject verbal report, and occurrence of AEs and to review subject instructions for study drug dosing.

2.2 Schedule of Assessments for Cohorts B/C/D

	Screening Period	Baseline Visit	Treatment Period		Follow-up/ET
Visit Number	**1**	**2**	**3**	**4**	**5**
Study Day[1]	**-45 to -1**	**0 to 1 (24-h profile)**[2]	**8**[3]	**14 to 15 (24-h profile)**[2]	**Last dose + 30 days**[3]
Informed consent	X				
Inclusion and exclusion criteria	X				
Demography	X				
Medical history	X				
Prior medications from past year	X				
Concomitant medications[4]	X	X	X	X	X
Diary	**Run-in Period (Day -14 to -1)**[5]	X[6]	X[6]	X[6]	
Vital signs and body weight	X	X	X	X	X

[1] All visits should be performed on the indicated study days. In cases where this is not possible, the following visit windows apply: ±2 days for Visits 3 and 4, ±7 days for Visit 5.
[2] These are inpatient visits. During each inpatient visit, serial blood samples will be drawn over the course of 24 hours from 10a on the first day of the visit to 10a on the second day of the visit. It is recommended that subjects arrive by approximately 8a on the first day of each inpatient visit to allow time for check-in and study assessments before the 10a blood draw.
[3] These are morning outpatient visits. It is recommended that these visits be scheduled for approximately 8a to allow time for all laboratory assessments to be completed before the 10a blood draw and the 10a dose of study drug (at Visit 3).
[4] Subjects should be on a stable regimen of glucocorticoid replacement for a minimum of 30 days before baseline and throughout the treatment period. Subjects who take a dose of glucocorticoid medication in the morning when they rise should be instructed to hold this dose on the mornings of all study visits until after morning laboratory assessments have been completed.
[5] During the 2-week diary run-in period, which will occur during screening, subjects will document in a paper diary each dose of glucocorticoid medication taken, the time of each meal, and the time they went to bed and woke up each day.
[6] During the treatment period, subjects will document in a paper diary the same information as during the run-in period, plus each dose of study drug taken and whether it was taken with a standardized snack or meal.

	Screening Period	Baseline Visit	Treatment Period		Follow-up/ET
Visit Number	**1**	**2**	**3**	**4**	**5**
Study Day[1]	**-45 to -1**	**0 to 1 (24-h profile)[2]**	**8[3]**	**14 to 15 (24-h profile)[2]**	**Last dose + 30 days[3]**
Physical examination[7]	X	X	X	X	X
12-lead ECG	X	X		X	X
Testicular ultrasound for males	X				
M.I.N.I. Version 7.0.2	X				
BDI-II	X	X		X	X
C-SSRS	X	X		X	X
HADS		X		X	X
CAH signs and symptoms interview	X	X	X	X	X
Acute SF-36	X	X	X	X	X
PGIC			X	X	X
Hepatitis B & C and HIV screening	X				
Pregnancy test (WOCBP only)[8]	X	X		X	X
Clinical laboratory assessments[9]	X	X	X	X	X
Serum 17-OHP for screening	X[10]				
Genetic sample[11]		X			

[7] A full physical examination will be conducted at Visit 1 (screening), Visit 2 (baseline), and Visit 4 (second 24-hour visit). Male subjects should have a testicular exam as part of the physical examination at Visits 2 and 4. Female breast and genitalia examinations are not required. An abbreviated physical examination will be conducted at Visits 3 and 5. Height only needs to be collected at screening.
[8] Serum pregnancy test at screening; in-clinic urine pregnancy test at subsequent visits specified.
[9] Clinical laboratory assessments include hematology, clinical chemistry, urinalysis, plasma renin, aldosterone, thyroid-stimulating hormone, T3, T4, luteinizing hormone, follicle-stimulating hormone, sex hormone–binding globulin, inhibin B, and, for females only, estradiol, prolactin, and progesterone.
[10] During screening, subjects should take any morning glucocorticoid medication after their blood draw to allow for an unimpeded assessment of 17-OHP.
[11] Genetic testing is optional for those with previous genetic testing and/or for those who have agreed to participate in the genetic sub-study (separate consent required).

	Screening Period	Baseline Visit	Treatment Period		Follow-up/ET
Visit Number	**1**	**2**	**3**	**4**	**5**
Study Day[1]	**-45 to -1**	**0 to 1 (24-h profile)**[2]	**8**[3]	**14 to 15 (24-h profile)**[2]	**Last dose + 30 days**[3]
24-h blood sampling for PK and/or PD[12]		X[13]		X[14]	
Abbreviated PK/PD[12,15]			X		X
24-hour urine collection[16]		X		X	
Blood sample for exploratory biomarkers[17]		X	X	X	X
Salivary 17-OHP[18]		X	X	X	X
Dispense study drug		X[19]			

[12] For each PD sample, the concentrations of 17-OHP, ACTH, androstenedione, testosterone, and glucocorticoids (cortisol/prednisolone/dexamethasone, depending on what the subject is taking) will be measured.
[13] At the baseline inpatient visit, only a baseline PD profile will be obtained. The first serial timepoint for baseline PD will be at the time the AM dose of study drug would be (10a in Cohorts B and C). Subsequent timepoints will be at 2, 3, 4, 5, 6, 7, and 8 hours after the time corresponding to the AM dose, then every 2 hours thereafter through the time corresponding to the PM dose, and at 4, 5, 6, and 8 hours after the time corresponding to the PM dose, then every 2 hours thereafter through the time corresponding to the next AM dose. Thus, for Cohorts B and C, serial blood samples will be drawn for PD measurements at 10a, 12p, 1p, 2p, 3p, 4p, 5p, 6p, 8p, and 10p on Day 0 and 2a, 3a, 4a, 6a, 8a, and 10a on Day 1. Subjects will take their first dose of study drug at the end of the baseline inpatient visit, before discharge.
[14] At the second inpatient visit, both PK and PD profiles will be obtained. The first serial timepoint for PK/PD will be immediately before the AM dose. Subsequent timepoints will be at 2, 3, 4, 5, 6, 7, and 8 hours after the time corresponding to the AM dose, then every 2 hours thereafter through the time corresponding to the PM dose, and at 4, 5, 6, and 8 hours after the time corresponding to the PM dose, then every 2 hours thereafter through the time corresponding to the next AM dose. Thus, for Cohorts B and C, serial blood samples will be drawn for concentrations of SPR001 and PD measurements at the following timepoints: pre-dose and at 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours post-dose after the 10a dose and at 4, 5, 6, 8, 10, and 12 hours after the 10p dose. (The 12-h sample for the 10a dose will be the same as the pre-dose sample for the 10p dose.)
[15] For each abbreviated PK/PD assessment, a single blood sample should be drawn at approximately 10a.
[16] 24-hour urine will be collected in 2 aliquots: the first aliquot from the time corresponding to the AM dose to immediately before the time corresponding to the PM dose, the second aliquot from the time corresponding to the PM dose to immediately before the time corresponding to the subsequent AM dose. Thus, for Cohorts B and C, the first aliquot will be collected from 10a to 10p, and the second aliquot will be collected from 10p to 10a of the following morning. Urine concentrations of 17-OHP and free cortisol will be measured. Urine concentrations of SPR001 and exploratory urine biomarkers may also be measured.
[17] A single blood sample will be drawn at approximately 10a for exploratory biomarkers.
[18] Salivary 17-OHP should be collected at around the same time during the morning of each visit (between approximately 8a to 10a).

	Screening Period	Baseline Visit	Treatment Period		Follow-up/ET
Visit Number	**1**	**2**	**3**	**4**	**5**
Study Day[1]	**-45 to -1**	**0 to 1 (24-h profile)**[2]	**8**[3]	**14 to 15 (24-h profile)**[2]	**Last dose + 30 days**[3]
AE review		**X**	**X**	**X**	**X**

Abbreviations: 17-OHP = 17-hydroxyprogesterone; ACTH = adrenocorticotropin hormone; AE = adverse event; BDI-II = Beck Depression Inventory-II; CAH = congenital adrenal hyperplasia; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; HADS = Hospital Anxiety and Depression Scale; HIV = human immunodeficiency virus; MINI = Mini International Neuropsychiatric Interview; PD = pharmacodynamics; PGIC = Patient Global Impression of Change; PK = pharmacokinetics; SF-36 = Short Form 36; WOCBP = women of childbearing potential.

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[19] The first dose of study drug will be taken at the end of the baseline inpatient visit, after all baseline assessments have been completed and before discharge. Subjects will be discharged with a 2-week supply of study drug.

3 INTRODUCTION

3.1 Study Rationale

Patients with congenital adrenal hyperplasia (CAH) whose signs, symptoms, and androgen levels are not adequately controlled by physiological glucocorticoid replacement (5.3 to 6.1 mg/m^2/day secretion) require additional therapy (Esteban et al. 1991; Kerrigan et al. 1993). Since elevated adrenocorticotropin hormone (ACTH) is the primary driver for adrenal steroid production in patients with CAH, blocking ACTH synthesis using a corticotropin-releasing factor type-1 (CRF_1) receptor antagonist may reduce adrenal steroid production while avoiding the need for supraphysiologic doses of glucocorticoids. In one study, a CRF_1 antagonist produced dose-dependent reductions of ACTH and 17-hydroxyprogresterone (17-OHP) in patients with classic CAH (Turcu et al. 2016). These promising results provide a rationale for investigating the use of CRF_1 receptor antagonists combined with physiologic (versus supraphysiologic) doses of glucocorticoids and mineralocorticoids for the treatment of classic CAH.

3.2 Background

3.2.1 Overview of Congenital Adrenal Hyperplasia

CAH is a deficiency of critical enzymatic activity within the steroidogenic pathways that leads to the biosynthesis of cortisol (White and Speiser 2000; Bachelot et al. 2008). CAH is chronically debilitating because of the development of adrenal insufficiency, precocious puberty, impaired growth, virilization in females, hirsutism, seborrhea, amenorrhea, irregular menses, impaired fertility, testicular adrenal rest tumors (TART), fatigue, anxiety, depression, hyponatremia, hyperkalemia, dehydration, and hypotension, all of which can occur even in the context of routine glucocorticoid (± mineralocorticoid) replacement.

The most common cause of CAH, accounting for over 90% of cases, is mutation of the *CYP21A2* gene, which encodes the P450c21 enzyme, commonly known as 21-hydroxylase (White and Speiser 2000; Bachelot et al. 2008; Auchus 2015; Doleschall et al. 2014). A deficiency in 21-hydroxylase disrupts the pathway involved in cortisol and aldosterone production. Additionally, impaired cortisol production removes negative feedback to the hypothalamus and pituitary gland, which amplifies the secretion of corticotropin-releasing factor (CRF) and ACTH, respectively. The increased CRF- and ACTH-mediated drive results in hyperplasia of the adrenal cortex and, consequently, the overproduction of cortisol precursors such as 17-OHP, which get funneled into the biosynthetic pathway responsible for adrenal androgen production.

Approximately 75% of patients with CAH have severe aldosterone deficiency ("salt-wasting CAH"). Salt-wasting forms of CAH are characterized by low serum aldosterone concentrations, hyponatremia, hyperkalemia, and elevated plasma renin activity indicating hypovolemia. Affected individuals lose large amounts of sodium in their urine, which can be life threatening in early infancy. The remaining 25% of patients have simple virilizing forms of CAH and produce sufficient aldosterone to avoid neonatal adrenal crisis.

Complete deletions, large gene conversions, and nonsense or frame-shift mutations that completely ablate *CYP21A2* activity typically result in salt-wasting forms of CAH. Mutations

resulting in even 1% to 2% residual enzyme activity allow sufficient aldosterone production and lead to simple virilizing forms of CAH. 21-hydroxylase deficiency represents >90% of all CAH cases, though several additional genes responsible for encoding other critical enzymes contribute to 5% to 10% of CAH cases: *CYP17A1, HSD3B2, CYP11B1,* and *POR*) (Turcu and Auchus 2015).

3.2.2 Diagnosis

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 the newborn period (Falhammar et al. 2015). A 17-OHP level >300 nmol/L is indicative of untreated CAH, and the patient is then generally genotyped to assist in treatment approaches (Falhammar et al. 2015). A genetic screening test is available and commonly used for confirmation (Choi et al. 2016).

3.2.3 Current Standard of Care

Treatment of CAH is centered around providing pharmacologic (supraphysiologic) doses of glucocorticoids (eg, hydrocortisone) to replace cortisol. In patients with the salt-wasting form of CAH, mineralocorticoids (eg, fludrocortisone) are used to replace aldosterone. Before weaning, additional salt supplements (NaCl) are provided to prevent a potentially lethal salt-losing crisis.

The clinical management of CAH is a 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). Under-treatment carries the risk of adrenal crisis and allows increased adrenal androgen production, which contributes to the development of TART, infertility, precocious puberty, female virilization, dehydration, and hypotension. In contrast, overtreatment may suppress growth, increase blood pressure, and cause iatrogenic Cushing's syndrome. Over a lifetime, the treatment of patients with CAH shifts from an emphasis on normal growth and development of children and adolescents to long-term health concerns in the adult, including obesity, hypertension, infertility, metabolic abnormalities, cardiovascular disease, and overall diminished quality of life (Auchus 2015). In one study, patients with salt-wasting CAH had a greater risk for mortality, with a mean age of death of 41.2 years. The causes of death were adrenal crisis (42%), cardiovascular disease (32%), cancer (16%), and suicide (10%) (Falhammar et al. 2014).

Current challenges in the care of patients with CAH include the narrow therapeutic window for glucocorticoid therapy. As evidence-based treatment guidelines are only beginning to be developed (Reisch 2015), overall treatment effectiveness for patients with CAH is poor (Mnif et al. 2012; Bachelot et al. 2015), with less than one-third of CAH patients achieving 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).

3.2.4 SPR001 for the Treatment of CAH

SPR001 is intended for treatment of CAH based on its ability to reduce the hypothalamic drive of CRF on the CRF_1 receptors located on the pituitary gland, thereby reducing ACTH overproduction and consequent 17-OHP excess. SPR001 binds to CRF_1 receptors with high affinity and specificity and blocks CRF_1-mediated G protein–coupled receptor function.

Antagonism of CRF_1 receptors has been shown to decrease the synthesis and release of ACTH and subsequently attenuate the production and release of adrenal androgens.

Thus, SPR001 is intended to allow for physiologic (versus supraphysiologic) glucocorticoid administration in patients with CAH, reducing 17-OHP buildup and androgen excess while avoiding symptoms associated with high-dose glucocorticoid therapy and iatrogenic Cushing's syndrome. Meaningful reductions in ACTH and 17-OHP following oral administration of a CRF_1 receptor antagonist in CAH patients have demonstrated target engagement and proof of principle in this disorder (Turcu et al. 2016). These promising data provide a rationale for additional investigations of SPR001, a small-molecule CRF_1 receptor antagonist, for the treatment of classic CAH, in combination with physiologic doses of glucocorticoid replacement.

3.3 Benefit/Risk Assessment

The safety of SPR001 was established in nonclinical toxicology studies and in 2 clinical studies conducted in healthy volunteers.

The SPR001 nonclinical toxicology program includes repeat-dose range-finding and definitive general toxicity studies in rats and dogs of up to 3 months in duration using the clinically relevant route (oral) and schedule (once daily) of administration. In addition, fertility studies were conducted separately in male and female rats. A complete standard genotoxicity testing battery that included in vitro bacterial reverse mutation and chromosome aberration assays and an in vivo (rat) bone marrow micronucleus assay was performed. Exploratory and definitive embryo-fetal development studies in rabbits and a bovine corneal opacity and permeability assay were also conducted.

SPR001 was shown to be safe and well tolerated in healthy adult subjects (ages 21 to 65 years) in multiple Phase 1 clinical studies. In the single-dose study, diarrhea and headache were experienced by a small number of subjects. These events were mild or moderate in severity. In the multiple-dose study, dyspnea, rhinorrhea, palpitations, and headache were experienced by a small number of subjects. No clinical safety concerns with SPR001 were raised, as there were no clinically significant alterations in safety laboratory values, vital signs, or electrocardiograms (ECGs).

Laboratory abnormalities in liver function tests (LFTs) have been observed at significantly higher doses in nonclinical studies. However, these events were not observed in the human trials.

Reversible testicular effects (degeneration/atrophy) were noted in rats and dogs treated with high-dose SPR001 (2,000 mg/kg/day). However, male reproductive studies in rodents showed no impairment in fertility at the highest dose tested (1,000 mg/kg/day). Additionally, there were no effects on clinical pathology markers of testicular function (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) when SPR001 was administered to healthy male volunteers at doses up to 200 mg per day for 14 consecutive days. Measures of testicular function will be monitored throughout the study.

SPR001-induced effects on the thyroid gland were noted in dogs after 13 weeks of high-dose (2,000 mg/kg/day) treatment, though not in any of the other nonclinical studies. Clinical pathology parameters of thyroid function (eg, T4, T3, thyroid-stimulating hormone [TSH]) have

not been evaluated in SPR001-treated humans to date but will be monitored throughout the study.

Evidence from nonclinical and early clinical studies are suggestive of a potential therapeutic benefit of SPR001 in the treatment of CAH involving CRF_1 receptor antagonism, supporting the continued clinical investigation of SPR001 for treatment of CAH.

4 OBJECTIVES

The primary objectives of the study are:

- To evaluate the safety of SPR001 in subjects with CAH
- To assess the efficacy of SPR001 in subjects with classic CAH as measured by percent and absolute change in 17-OHP compared to baseline

The secondary objectives of the study are:

- To explore the dose(s) of SPR001 that cause pharmacodynamic (PD) changes in plasma concentrations of ACTH, androstenedione, and testosterone, as measured by the absolute and percent change from baseline by dose
- To determine pharmacokinetics (PK) of SPR001 in subjects with CAH
- To explore potential relationships between PK and PD

The exploratory objective of the study is:

- To explore the dose(s) of SPR001 that cause changes in PD biomarkers in urine, as measured by the absolute and percent change from baseline by dose

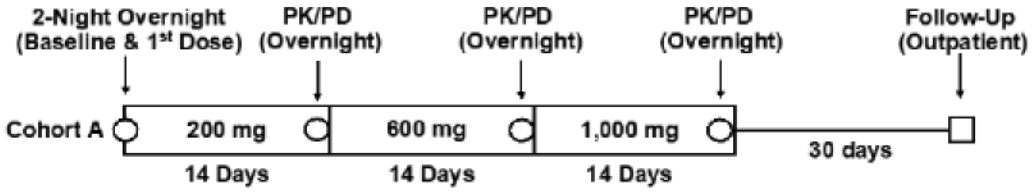
5 STUDY DESIGN

5.1 Overall Design

5.1.1 Cohort A

Cohort A is a 6-week, multiple-dose, intra-subject dose-escalation study of SPR001 in approximately 9 adults with CAH. The design of Cohort A is schematized in Figure 5-1. Subjects in Cohort A will undergo dose escalation through 3 dose levels of SPR001, beginning with 200 mg/day for 2 weeks, then escalating to 600 mg/day for 2 weeks, then escalating to 1000 mg/day for 2 weeks. If a subject develops dose-limiting toxicity (DLT), the subject's dose may be reduced according to Section 8.1. During the treatment period, SPR001 will be administered as an oral daily dose at 10p (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack. The 6-week treatment period will be followed by a 30-day washout and safety follow-up period.

Figure 5-1. Cohort A Design



The Schedule of Assessments for Cohort A is provided in Section 2.1. Subjects will have a total of 5 overnight visits for PK/PD profiling, with serial blood samples collected over the course of 10 hours during each overnight visit. The 5 overnight visits will consist of a baseline overnight hormone profile 1 day before the first dose of study drug, an overnight profile with the first dose of study drug, and overnight profiles at Day 14 (steady state) of each dose period. Subjects will have a final follow-up outpatient visit 30 days after the last dose of study drug.

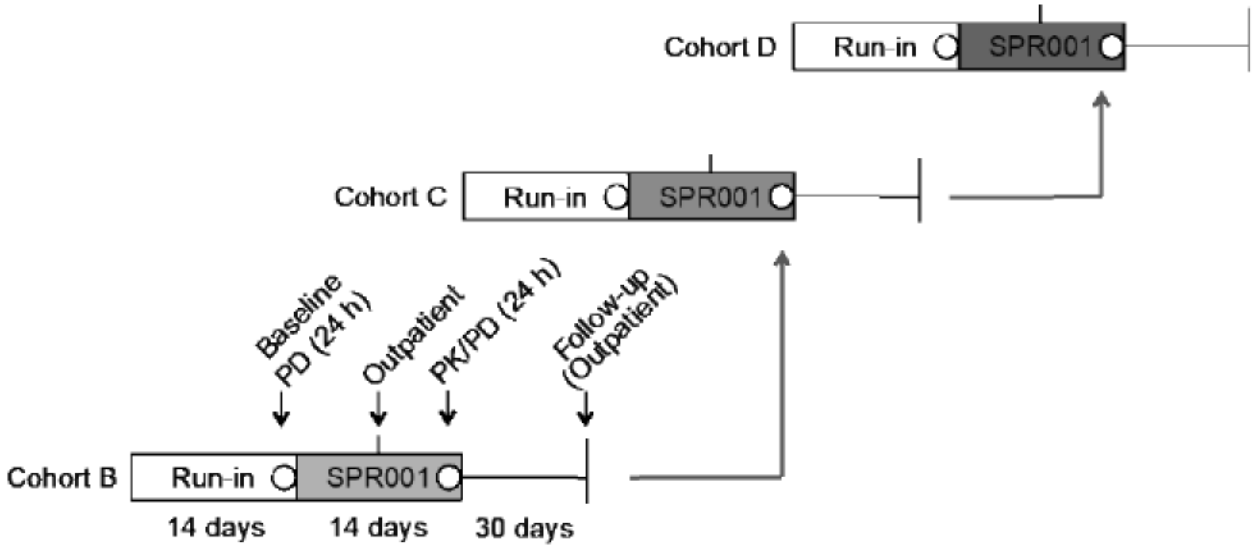
Based on review of the available safety, PK, and PD data from Cohort A and the recommendations of the safety review committee (SRC), an adaptive multiple ascending dose (MAD) sequence of 3 cohorts is planned after completion of enrollment in Cohort A.

5.1.2 Cohorts B/C/D

An adaptive MAD design with 3 sequential cohorts (Cohorts B, C, and D) is planned to evaluate the safety, PK, and PD of various SPR001 dosing regimens and to identify an optimal dose regimen. The design of Cohorts B/C/D is schematized in Figure 5-2. Each cohort will undergo a 2-week run-in period, a 2-week treatment period, and a 30-day washout and safety follow-up period. During the run-in period, which will occur during screening, subjects will document in a paper diary each dose of glucocorticoid medication taken, the time of each meal, and the time they went to bed and woke up each day, to ensure compliance with background glucocorticoid regimens and the stability of their daily routine.

Each cohort will initially enroll 3 subjects and may later enroll 3 more subjects based on interim data from the first 3 subjects, for a total of 6 subjects per cohort. However, if safety, PK, and PD results from 6 subjects are inconclusive, a cohort may be expanded up to a maximum of 12 subjects. Cohort B will receive study drug at 200 mg twice daily (BID). Cohort C will receive study drug at 100 mg BID. For BID regimens, subjects will take a dose at 10a and a dose at 10p, either with a meal or 5 to 15 minutes after consumption of a standardized snack. For Cohort D, the dose level and the frequency and timing of dosing will be determined based on interim data from the previous cohorts. However, the dose level of Cohort D will be capped at 800 mg/day. Additionally, the steady-state exposure will be estimated for each dose cohort before initiating higher dose cohorts to ensure that the area under the concentration-time curve (AUC) over a 24-hour interval does not exceed a maximum of 100,000 ng·h/mL. Thus, dosing in this study will not exceed ***either*** a maximum dose of 800 mg/day ***or*** a maximum 24-hour AUC of 100,000 ng·h/mL, whichever limit is equivalent to a lower dose.

Figure 5-2. Cohort B/C/D Design



Decisions regarding continuation or suspension of dosing, cohort expansion, and the dose level and timing of doses for the next cohort will be made by the Sponsor after the SRC reviews interim safety, PK, and PD data and provides its recommendation. Interim data will be analyzed for the first 3 subjects in each cohort after each subject completes the 2 weeks of SPR001 dosing and on an ongoing basis. In particular, the occurrence of any clinically significant adverse event (AE) will receive special consideration and will be reported to the SRC within 1 day of awareness for immediate review. Clinically significant AEs include but are not limited to DLTs (Section 9.3.9), serious adverse events (SAEs) (Section 9.3.3), AEs leading to study drug discontinuation, and AEs of special interest (Section 9.3.4), all considered at least possibly related to study drug.

Based on recommendations from the SRC and the safety, tolerability, and PK/PD profile of SPR001, the Sponsor may implement any of the following actions:

- If ≤1 subject among the first 3 subjects of a cohort experiences a clinically significant AE, the Sponsor may elect to continue with enrollment of an additional 3 subjects into that cohort. If ≤1 subject among the 6 subjects of a cohort experiences a clinically significant AE, the Sponsor may then elect to proceed with enrollment of the next cohort.
- If exactly 2 subjects among the first 3 subjects in a cohort experience a clinically significant AE, the Sponsor will suspend dosing in that cohort, and the SRC will make recommendations on next steps.
- If exactly 2 subjects among the 6 subjects of a cohort experience a clinically significant AE, the Sponsor may elect to enroll an additional 3 subjects into that cohort at the same dose. If no additional clinically significant AEs occur, the Sponsor may then elect to proceed with enrollment of the next cohort.

- If ≥3 subjects in a dose cohort experience a clinically significant AE, the Sponsor will suspend dosing and enrollment in that cohort and/or any further dose escalation in the study. Additional subjects may be enrolled at the previous or an intermediate dose.
- If data from the first 3 subjects in a cohort indicate suboptimal drug exposure and efficacy (based on PK and PD biomarkers after 2 weeks of SPR001 dosing) and there are no significant safety issues such as clinically significant AEs, the Sponsor may elect to discontinue further enrollment in that cohort and proceed directly to the next cohort.
- If safety, PK, and PD data from 6 subjects in a cohort are inconclusive, the Sponsor may elect to increase enrollment of a cohort and/or repeat a cohort, up to a maximum of 12 subjects treated at a single dose level of SPR001 under this protocol.

Additionally, the Sponsor may elect to modify the timing of SPR001 dosing to enhance PD effects on CAH biomarkers of interest. The Sponsor may also elect to modify existing glucocorticoid regimens in order to (1) better isolate the PD effects of SPR001 on CAH by minimizing any confounding effects of existing background therapies and/or (2) evaluate for any potential drug-drug interactions between SPR001 and existing glucocorticoid regimens.

The Schedule of Assessments for Cohorts B/C/D is provided in Section 2.2. Subjects will have 2 inpatient visits for PK/PD profiling, one for baseline PD profiling after the 2-week run-in period and before starting study drug and one for both PK and PD profiling after 2 weeks on study drug. Serial blood samples will be collected over the course of 24 hours during each inpatient visit. Subjects will also have a pre-dose morning outpatient visit at Day 8 and a follow-up outpatient visit 30 days after the last dose of study drug.

Subjects will be assigned to cohorts on the basis of their order of entry into the study. A subject may enroll in >1 cohort if the subject experienced no clinically significant AE in the previous cohort and the Sponsor provides approval. For subjects who do participate in >1 cohort, the final safety follow-up visit of the subject's previous cohort (which occurs after a 30-day washout of study drug) may serve as the screening visit of the subject's next cohort.

5.2 Safety Review Committee and Adaptive Dose Escalation

An SRC comprised of appropriate medical and clinical representatives will review safety, PK, and PD data on an ongoing basis throughout the study. Decisions regarding intra-subject dose escalation in Cohort A and decisions regarding continuation or suspension of dosing, cohort expansion, and dosing paradigm in subsequent cohorts will be made by the Sponsor after the SRC reviews interim safety, PK, and PD data and provides its recommendation. In addition to clinically significant AEs (Section 9.3.10) occurring during the treatment period, late and chronic toxicities will be evaluated and taken into account in determining the safety of each dose level for future studies and the need for additional cohorts in this study. Decisions will be communicated promptly to all participating study personnel and applicable regulatory authorities/IRBs. A full explanation of the rationale and details describing such decisions will be provided in the form of an administrative letter and documented in the trial master file. A separate charter will detail the responsibilities of the SRC.

5.3 Participant Discontinuation

If a subject prematurely discontinues treatment (and associated steady-state assessments), the subject is considered a dropout. Subjects prematurely discontinued from the study may be replaced to ensure adequate numbers of evaluable subjects. The decision to replace a withdrawn subject will be made at the discretion of the Sponsor and documented.

5.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all weeks of treatment assigned to his/her cohort, including the final overnight PK/PD assessment. The end of the study is defined as the date of the last follow-up visit of the last participant in the study.

5.5 Scientific Rationale for Study Design

The study design includes both intra-subject dose escalation in Cohort A and inter-cohort dose escalation in Cohorts B/C/D. Intra-subject dose escalation in Cohort A is being used to gain an understanding of whether a fixed dose level can be used in future studies, or whether subject-specific titration will be needed based on individual characteristics. The adaptive MAD design in Cohorts B/C/D is an efficient way to explore an additional set of dose levels and regimens in order to rapidly identify an optimal SPR001 dose. This trial design is intended to minimize exposure at sub-therapeutic doses and reduce study burden on subjects with CAH. The washout period will allow for analysis of any hypothalamic-pituitary-adrenal (HPA) axis rebound after ceasing study medication and will inform the design of future trials (eg, randomized withdrawal design).

The study design in Cohorts B/C/D also features a 2-week diary run-in period and two 24-hour inpatient visits. Participation in a clinical trial often changes subject behavior. In the case of CAH patients participating in this study, behavior changes may include improved compliance with background glucocorticoid medications and alterations in daily routine (such as changes to meal times and sleep schedules) to accommodate the SPR001 dosing schedule; such changes may produce effects on PD biomarkers independent from SPR001. The diary run-in period allows subjects to acclimate to study participation for 2 weeks before the collection of samples for the baseline PD profile and provides for more accurate and stable baseline data before initiating 2 weeks of active therapy with SPR001. The 24-hour PK profile will provide complete diurnal information on SPR001 exposure, which is appropriate to drug administered in a split dose. The 24-hour PD profile will provide complete diurnal information on the circadian rhythm of PD biomarkers, which will inform the timing and frequency of dosing in this and future studies.

The maximum concentration (C_{max}) of SPR001 in plasma occurred approximately 5 hours after dosing in the Phase 1 studies in healthy volunteers. Therefore, a dose of SPR001 before bedtime may achieve peak study drug concentration at the time of day when most adrenal androgens are produced. Since the Phase 1 studies showed minimal absorption in the fasted state, subjects will be instructed to take study medication following consumption of a meal or standardized snack.

The sample size of 9 subjects in Cohort A and 3 to 6 subjects each in Cohorts B/C/D is anticipated to provide sufficient data for PK analysis based on previously conducted Phase 1 studies that assessed PK in healthy volunteers. This is a sample size that can be reasonably

expected to provide an estimate of safety and effectiveness while maintaining feasible subject recruitment goals in this rare disease population.

5.6 Justification for Dose

An optimal dose regimen for SPR001 should provide a level of drug exposure that is both potentially efficacious (see Section 5.6.1) and within the potential safe exposure limit for SPR001 (see Section 5.6.2).

5.6.1 Potentially Efficacious Exposure Level for SPR001

A primary objective of this study is to test the efficacy of SPR001 in subjects with CAH. In order to test the efficacy of SPR001 and to achieve an optimal dose regimen, SPR001 should be administered at a potentially efficacious (and safe) dose. Nonclinical studies provide estimates of the SPR001 exposure required to achieve a potentially efficacious dose.

In a rat ex vivo CRF_1 receptor occupancy study, an exposure of 531 ng/mL SPR001 produced 90% CRF_1 receptor occupancy in rat brain tissue. Associated behavioral and pharmacology studies showed that this level of exposure to SPR001 produced functional blockade of the CRF_1 receptor.

In an in vitro functional cyclase assay in HEK293 cells expressing human CRF_1 receptor, SPR001 was a potent inhibitor of CRF-stimulated cyclic adenosine monophosphate (cAMP) accumulation, with an equilibrium binding constant (K_b) of 5.19 nM (equivalent to approximately 2.18 ng/mL). SPR001 is highly lipophilic (logP >4) and thus highly protein bound in plasma (approximately 99.8%). At steady state, the approximately 0.2% of SPR001 that is free in plasma is anticipated to be at equilibrium with the concentration of SPR001 at the site of action (ie, CRF_1 receptors in the pituitary). If approximately 0.2% of SPR001 is free to bind with the CRF_1 receptor, it is anticipated that an average steady-state plasma concentration of SPR001 at or above approximately 1100 ng/mL will be required to match or exceed the K_b of approximately 2.18 ng/mL.

5.6.2 Potential Safe Exposure Limit for SPR001

Considerations in establishing a potential safe exposure limit for SPR001 in subjects with CAH include the following:

1) nonclinical NOAELs determined in toxicology studies with healthy rats and dogs;

2) the nature, severity, and reversibility of the specific toxicities observed in these toxicology studies;

3) the distinction between the animals with normal hormone function used in these toxicology studies and the CAH patients with abnormally elevated hormone levels for whom androgen reduction is a goal of therapy; and

4) the ability to monitor relevant toxicities in a clinical setting.

Nonclinical NOAELs were determined in 3-month toxicology studies in rats and beagle dogs in which oral SPR001 was administered once daily for 91 consecutive days at doses of 0, 5, 20 (rats only), 70 (dogs only), or 2,000 mg/kg/day. SPR001 was generally well tolerated at all dose levels administered. SPR001-related adverse toxicological findings occurred only at the highest dose of 2000 mg/kg/day and consisted of mild microscopic observations in the male reproductive tract of both species (spermatocyte/spermatid degeneration in rats and seminiferous tubule

degeneration/atrophy in dogs) and mean body weight loss in dogs. The testicular findings were fully reversible within 6 weeks post-treatment. Thus, the NOAELs in these studies were considered to be 20 mg/kg/day for male rats, 2000 mg/kg/day for female rats, and 70 mg/kg/day for both male and female dogs. Note the relatively large dosage gap between the 20 mg/kg/day (rats) or 70 mg/kg/day (dogs) NOAELs and the 2000 mg/kg/day dose at which adverse findings occurred. The systemic exposure parameters (C_{max} and AUC_{0-24}) corresponding to these nonclinical NOAEL doses are shown in Table 5-1.

Subsequent fertility studies were conducted separately in male and female rats administered SPR001. In the male rat fertility study, male rats were administered oral SPR001 once daily for 85 to 87 days (from 70 days before to ≤4 days after the mating period) at a dose of 0, 5, 20, or 1000 mg/kg/day. There were no adverse toxicological findings and no effects of SPR001 on reproductive performance in treated males (mean day of mating, mating and fertility indices, conception rates) or the ovarian and uterine parameters of untreated females mated with the treated males. In the female rat fertility study, female rats were administered oral SPR001 once daily from 14 days before mating to gestation day 7 at a dose of 0, 20, 300, or 1000 mg/kg/day. No adverse effects of SPR001 were observed on survival, clinical findings, body weights or body weight change, food consumption, estrous cyclicity, reproductive performance and fertility, gestation day 13 uterine implantation data, reproductive organ weights, or macroscopic findings. In both of these studies, the NOAEL was considered to be 1000 mg/kg/day, the highest dose level evaluated. Systemic exposure for male rats dosed at the 1000 mg/kg/day NOAEL in this study is shown in Table 5-1.

Table 5-1. Systemic Exposure Parameters for SPR001 in Rats and Dogs at Identified NOAELs

Species Sex	NOAEL (mg/kg/day)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)
Rat			
Male[1]	20	2,901	30,536
Male[2]	1000	13,812	229,078
Female[1]	2000	19,122	333,925
Dog			
Male[1]	70	2,223	29,364
Female[1]	70	2,880	34,185

Abbreviations: AUC_{0-24} = area under the concentration-time curve from 0 to 24 hours after dosing; C_{max} = maximum concentration; NOAEL = no-observed-adverse-effect level.
[1] Data from Day 90 of 91-day definitive toxicology studies.
[2] Data from Day 69 of 85-to-87–day fertility study.

Given these nonclinical exposures at the identified NOAELs, and per Food and Drug Administration (FDA) guidance, clinical doses of SPR001 in this study will be selected such that the steady-state AUC over a 24-hour interval does not exceed a maximum of 100,000 ng·h/mL.

The male reproductive tract findings in the 91-day toxicology studies occurred in the setting of animals with normal, rather than elevated, baseline hormone function. As a CRF_1 receptor antagonist, SPR001 is intended to reduce abnormally elevated ACTH concentrations in patients with CAH, leading to reductions in androgen and androgen precursor levels and, ultimately, improved clinical outcomes for CAH patients. 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 reductions in androgens outside of the normal range. In a CAH disease state, where baseline androgen levels are pathologically elevated, reductions in androgens are the goal of therapy and would be considered a positive, therapeutic effect. This distinction between healthy animals and CAH patients serves to further increase confidence that limiting clinical SPR001 exposure to a maximum AUC of 100,000 ng·h/mL will be safe for subjects with CAH.

Furthermore, extensive clinical monitoring for reproductive AEs and strict stopping criteria have been incorporated into this study. Any clinically significant abnormalities (including but not limited to changes in LH, FSH, inhibin B, sex hormone–binding globulin [SHBG], estradiol, progesterone, or prolactin) or any other changes in testicular function or menstrual cyclicity will trigger potential discontinuation of study drug. In Cohorts B/C/D, clinic visits will occur weekly during the 2-week treatment period (at baseline, Day 8, and the end of the treatment period).

5.6.3 Dosing in Cohort A

In Cohort A, SPR001 dosing will begin at 200 mg/day for 14 days, escalating for each subject to 600 mg/day for 14 days, then 1000 mg/day for 14 days if the subject experiences no DLT at the previous dose level. The starting dose regimen of 200 mg/day for 14 days was previously assessed in the repeat-dose Phase 1 Study I3C-FW-BLAB in healthy subjects and was well tolerated in that study. Table 5-2 shows the steady-state C_{max}, AUC_{0-24}, and C_{avg} for these healthy subjects after receiving 200 mg/day SPR001 for 14 days. It also shows the projected values of these parameters at the proposed higher doses in Cohort A if exposure is approximated to increase in a dose-proportional manner (by 3-fold for the 600 mg/day dose over the 200 mg/day dose and by 5-fold for the 1000 mg/day dose). All projected exposure parameters remain well below the nonclinical exposures experienced at even the most conservative NOAEL (see Table 5-1). The highest dose of 1,000 mg/day in Cohort A was selected to permit an interim safety review of Cohort A prior to utilizing potentially higher doses in Cohort B.

Table 5-2. Projected Clinical Systemic Exposure Parameters for SPR001 at Proposed Doses in Cohort A

Exposure Parameter	Actual Exposure[1] (Geometric mean, CV%)	Projected Exposures[2]	
	200 mg QD	600 mg QD	1000 mg QD
C_{max} (ng/mL)	314 (93)	942	1570
AUC_{0-24} (ng·h/mL)	2040 (98)	6120	10,200
C_{avg} (ng/mL)	85.0 (98)	255	425

Abbreviations: AUC_{0-24} = area under the concentration-time curve from 0 to 24 hours after dosing; BID = twice a day; C_{avg} = average concentration; C_{max} = maximum concentration; CV = coefficient of variability; NOAEL = no-observed-adverse-event level; QD = once a day.

[1] Exposure parameters in healthy adults after 14 days of SPR001 200 mg/day QD in Phase 1 Study I3C-FW-BLAB.
[2] Projections based on dose-proportionality of exposure.

5.6.4 Dosing in Cohort B and Beyond

In Cohorts B and C, the SPR001 dosing regimen will be modified from a once-daily to a twice-daily (BID) schedule. Subjects in Cohort B will receive SPR001 at 200 mg BID. A total daily dose of 400 mg/day administered as 200 mg BID is expected to provide daily exposure levels within boundaries that appear to be safe and well tolerated in Cohort A. Subjects in Cohort C will receive SPR001 at 100 mg BID. Relative to once-daily dosing in Cohort A, twice-daily dosing of SPR001 is expected to lower C_{max} levels and reduce peak-to-trough fluctuation.

In Cohort D, the dose level and the frequency and timing of dosing will be determined based on interim data from the previous cohorts. However, the dose level of Cohort D will be capped at 800 mg/day. Additionally, the steady-state exposure will be estimated for each dose cohort before initiating higher dose cohorts to ensure that the AUC over a 24-hour interval does not exceed a maximum of 100,000 ng·h/mL. At the cap of 800 mg/day, steady-state $AUC_{0\text{-}24h}$ is expected to remain well below the maximum of 100,000 ng·h/mL. Thus, dosing in this study will not exceed *either* a maximum dose of 800 mg/day *or* a maximum 24-hour AUC of 100,000 ng·h/mL, whichever limit is equivalent to a lower dose.

6 STUDY POPULATION

6.1 Inclusion Criteria

Subjects must meet all of the following criteria to be enrolled in this study:

1. Male and female subjects age 18 or older.
2. Documented historical diagnosis of classic CAH due to 21-hydroxylase deficiency based on documented genetic mutation in the CYP21A2 enzyme consistent with a diagnosis of classic CAH or historical documentation of elevated 17-OHP.
3. On a stable regimen of glucocorticoid replacement for a minimum of 30 days before baseline that is expected to remain stable throughout the study.
    - In Cohort A only, to standardize glucocorticoid replacement regimens and mitigate any potential for drug-drug interactions with SPR001, subjects who currently take any of their glucocorticoid doses after 6p (ie, at bedtime) will be required to take their evening glucocorticoid dose no later than 6p each day for at least 14 days before baseline.
4. Elevated adrenal androgens, defined as 17-OHP ≥800 ng/dL.
5. Male participants must agree to follow contraception guidelines (Section 12.5 [Appendix 5]) and refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study medication.
6. Female participants of childbearing potential must agree to follow appropriate contraception guidelines (Section 12.5 [Appendix 5]).

7. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all aspects of the trial.

6.2 Exclusion Criteria

Subjects will not be eligible for this study if they meet any of the following criteria:

1. Clinically significant unstable medical condition, medically significant illness, or chronic disease within 30 days of screening, including but not limited to:
   - A malignancy or less than 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 less than 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). Elevated antibody levels alone are not sufficient for exclusion.
2. Clinically significant psychiatric disorders either by history or from the Mini International Neuropsychiatric Interview (M.I.N.I.) conducted at Screening yielding 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. Beck Depression Inventory-II (BDI-II) score >29. For BDI-II scores >29 at screening, the site should discuss with the Medical Monitor to determine if the subject is eligible for this study.
4. At increased risk of suicide on the basis of the Investigator's judgment or the results of the Columbia-Suicide Severity Rating Scale (C-SSRS) conducted at Screening and Baseline (eg, C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior within the past 12 months).
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:
   - Clinically meaningful abnormal ECG results, in the opinion of the Investigator.
   - Fridericia-corrected QT interval (QTcF) >450 msec for male participants or QTcF >470 msec for female participants.
   - Alanine aminotransferase (ALT) >2x ULN.
   - Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
6. Known or suspected differential diagnosis of any of the other known forms of CAH, including non-classic CAH require Medical Monitor approval prior to enrollment.

7. A history that includes bilateral adrenalectomy or hypopituitarism.
8. Subjects who routinely work overnight shifts require Medical Monitor approval prior to enrollment.
9. Pregnant or nursing females.
10. Use of any other investigational drug within 30 days or 5 half-lives (whichever is longer) before initial screening.
11. As outlined in Section 12.8 (Appendix 8), required use of prohibited concomitant medications, including rosiglitazone 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 first dose of study drug. Those medications identified in Section 12.8 (Appendix 8) as sensitive substrates or substrates with narrow therapeutic ranges (metabolized by CYP3A4, 2C8, 2C9, or 2C19) should be discussed on a case-by-case basis with the Medical Monitor to determine if 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) prior to first dose of study drug.
12. Unable to understand and comply with the study procedures, unable to understand the risks involved, and/or unwilling to provide written informed consent.
13. Donation of blood within 60 days before first dose of study drug, or donation of platelets, white blood cells, or plasma within 15 days before first dose of study drug.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

Study drug must be consumed with food. Standardized snacks will be provided for all dosing days, as well as a list of acceptable alternative food combinations.

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

6.3.2 Caffeine, Alcohol, and Tobacco

During each inpatient visit for PK/PD profiling, participants should either abstain from or limit their ingestion of caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, or chocolate) for 5 hours before the first blood draw until after collection of the final PK/PD sample. Participants should ingest no more than 2 servings of any caffeine- or xanthine-containing products during each 24-hour PK/PD sampling period. Additionally, participants will abstain from alcohol for 12 hours before the first blood draw until after collection of the final PK/PD sample.

Participants who use tobacco products will be instructed that use of nicotine-containing products are not permitted while they are at the investigational site.

6.3.3 Activity

Ideally, participants should abstain from strenuous exercise for 8 hours before each inpatient visit. Participants may participate in light recreational activities during the study (eg, watching television, reading).

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered 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, including 17-OHP lab value if collected.

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 Medical Monitor:

- 17-OHP threshold criterion for participation in this study may be rescreened after 30 days if glucocorticoid replacement dose is reduced. During screening, subjects should take any morning glucocorticoid medication after their blood draw to allow for an unimpeded assessment of 17-OHP.
- Subjects with incompatible sleep patterns may be rescreened after 30 days if their sleep schedule stabilizes.
- Subjects on incompatible or excluded concomitant medications may be rescreened after an appropriate washout period (eg, 30 days or 5 half-lives, whichever is longer).

7 TREATMENT

7.1 Treatment Administered

Study Drug Name	SPR001
Formulation	SPR001 drug product is supplied for clinical trial use as white, hard-gelatin capsules containing either 50 mg or 200 mg of drug substance with no excipients.
Route of Administration	Oral
Packaging and Labeling	Study drug capsules are packaged in a high-density polyethylene (HDPE) bottle with a child-resistant cap and an induction foil seal. Capsules containing 50 mg drug substance are size 4 and packaged with 32 capsules per bottle in a 30-mL bottle with a 28-mm cap. Capsules containing 200 mg drug substance are size 1 and packaged either with 14 capsules per bottle (in a 30-mL bottle with a 28-mm cap) or with 60 capsules per bottle (in a 75-mL bottle with a 33-mm cap). Bottles are individually labeled with the protocol number, recommended storage conditions, the name and address of the Sponsor, Investigational Use Statement ("Caution: New Drug – Limited by Federal [USA] Law to Investigational Use"), and that the agent should be kept out of reach of children.

7.1.1 Cohort A

Subjects in Cohort A will be instructed to take study drug daily at 10p (or bedtime, if earlier), 5 to 15 minutes after consumption of a standardized snack. Subjects will take one 200-mg capsule daily during Weeks 1 and 2, three 200-mg capsules daily during Weeks 3 and 4, and five 200-mg capsules daily during Weeks 5 and 6.

7.1.2 Cohorts B and C

Subjects in Cohort B will be instructed to take one 200-mg capsule of study drug twice daily. Subjects in Cohort C will be instructed to take two 50-mg capsules of study drug twice daily. In both cohorts, study drug will be taken at 10a and 10p, either with a meal or 5 to 15 minutes after consumption of a standardized snack. For subjects who usually eat breakfast in the late morning and wish to take their 10a dose with breakfast, the Investigator should discuss the specific dosing situation with the Medical Monitor to determine whether the subject may take their 10a dose with breakfast. If a subject goes to bed earlier than 10p, the subject will take the 10p dose of study drug at bedtime.

7.1.3 Cohort D

The dosing regimen for Cohort D will be determined based on review of the data from earlier cohorts.

7.2 Treatment Assignment and Blinding

Subjects will be entered into a treatment dose/cohort based upon their order of enrollment. The study is an open-label trial with no randomization scheme.

7.3 Preparation/Handling/Storage/Accountability

Only participants enrolled in the study may receive study medication, and only authorized site staff may dispense or administer study medication. All study medication must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.

The Principal Investigator is responsible for study medication accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

7.4 Treatment Compliance

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

7.4.1 Study Diary

Subjects will be asked to maintain a paper diary for at-home use to capture daily information during the treatment period of every cohort and during the run-in period of Cohorts B/C/D. During the treatment period of Cohort A, subjects will document their ingestion of a standardized snack before study drug and the timing and dosage of each dose of study drug. During the run-in period in Cohorts B/C/D, subjects will document each dose of glucocorticoid

medication taken (see Section 7.5.1), the time of each meal, and the time they went to bed and woke up each day. During the treatment period of Cohorts B/C/D, subjects will document the same information as they did during the run-in period, plus each dose of study drug taken and whether it was taken with a standardized snack or meal. Participants will return their paper diary at each visit for review and/or collection, and either a new diary will be issued or the same diary will be returned for use during the next period. The Investigator is responsible for ensuring that subjects record the appropriate information in their diaries.

7.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, vitamins, and/or herbal or non-herbal supplements) that the participant is receiving at the time of screening or receives during the study 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, including those in use at screening and baseline and/or initiated during the course of the study, should be compared against the lists of excluded therapies and drugs of potential concern outlined in Section 12.8 (Appendix 8). Subjects should be instructed to contact the research site immediately any time a new medication is prescribed or required during the course of the study, including OTC cold and flu remedies, pain medications due to acute injuries or accidents, etc. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.5.1 Glucocorticoid Replacement Therapy

Subjects must be on a stable regimen of glucocorticoid replacement therapy for ≥30 days before baseline to be eligible for this study.

In Cohort A only, to standardize glucocorticoid replacement regimens and mitigate any potential for drug-drug interactions with SPR001, subjects will be required to take any evening glucocorticoid dose no later than 6p each day for at least 14 days before baseline and throughout the 6-week treatment period.

In Cohorts B/C/D, subjects should take their glucocorticoid medications according to their usual regimen unless otherwise specified (see below regarding morning doses of glucocorticoids on study visit days). Subjects in Cohorts B/C/D will document in a paper diary each dose of glucocorticoid medication that they take throughout the run-in and treatment periods, to ensure compliance with background glucocorticoid regimens.

For all cohorts, subjects who take a dose of glucocorticoid medication in the morning when they rise should be instructed to hold this dose on the mornings of all study visits until after morning laboratory assessments have been completed. During screening, subjects should also take any morning glucocorticoid medication after their blood draw to allow for an unimpeded assessment of 17-OHP. On non–study visit days during the study, subjects may take any morning dose of glucocorticoid replacement at their usual time.

7.6 Concomitant Medications of Concern

Rosiglitazone treatment is not permitted during the study as it could affect the patient's ACTH levels. Treatment with testosterone is also prohibited. In general, patients requiring ongoing treatment with rosiglitazone or testosterone should not be screened.

Section 12.8 (Appendix 8) outlines medications that are either excluded 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.

SPR001 is a moderate inhibitor of CYP3A4; therefore, drugs that are known strong inducers or inhibitors of CYP3A4 should be avoided during the study and require a washout period prior to screening, with the exception of stable daily doses of glucocorticoids and birth control. If an excluded 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 excluded agent is completed. If washout is appropriate, then a period of time equivalent to ≥5 drug half-lives or ≥30 days should transpire between the last dose of the excluded medication and the first dose of study drug.

Caution is also advised for drugs that are "sensitive substrates" of CYP3A4, 2C8, 2C9, and/or 2C19. Sensitive CYP substrates are drugs for which the plasma AUC has been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor, or drugs for which the AUC ratio in poor metabolizers vs extensive metabolizers is greater than 5-fold. These medications are also outlined in Section 12.8 (Appendix 8).

Lastly, caution is required for drugs metabolized by CYP3A4, 2C8, 2C9, and/or 2C19 that have narrow therapeutic ranges, whereby even small increases in their exposure levels could be associated with potential safety concerns (Section 12.8 [Appendix 8]).

If a medication is to be washed out, it should be stopped at least 30 days or 5 half-lives prior to dosing, whichever is longer. These medications cannot be resumed until after the safety follow-up visit.

It is important to note that many commonly used medications are listed in Section 12.8 (Appendix 8) 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). It is critical that each subject's concomitant medications are carefully compared to this list. Washout may be considered when appropriate, although in many cases washout will necessitate rescreening.

Patients should be advised to contact the site whenever any new medication is required, including both OTC and prescription drugs, and even when only to be used for a short period of time (eg, antibiotics, cold/flu remedies, gastrointestinal therapies, opioids or other pain relievers).

8 DOSE REDUCTION, DISCONTINUATION, STOPPING, AND WITHDRAWAL CRITERIA

8.1 Dose Reduction

For subjects who are unable to tolerate the protocol-specified dose level, dose adjustments are permitted in order to keep the subject on study. All such cases must be discussed with the Medical Monitor. At any time during the study, subjects with evidence of hypoadrenalism (eg, postural hypotension, nausea, abdominal pain) may forego dose escalation in Cohort A or have their dose reduced if the Investigator believes that an ongoing drug-related toxicity might jeopardize the subject's ability to complete the study.

For subjects who experience DLT (Section 9.3.9) at doses above 200 mg/day, a dose reduction in increments of 200 mg may be attempted. If this dose is also not tolerated, it is acceptable to revert to the previously tolerated dose for the remainder of the study.

If a subject cannot tolerate the 200 mg dose, the subject should be terminated from the study.

8.2 Renal Safety

During screening, eGFR will be determined by the preferred method of the central laboratory, accounting for subject-specific factors including sex and race. If eGFR values are determined to be below 60 mL/min/1.73 m^2, the subject will be ineligible to participate.

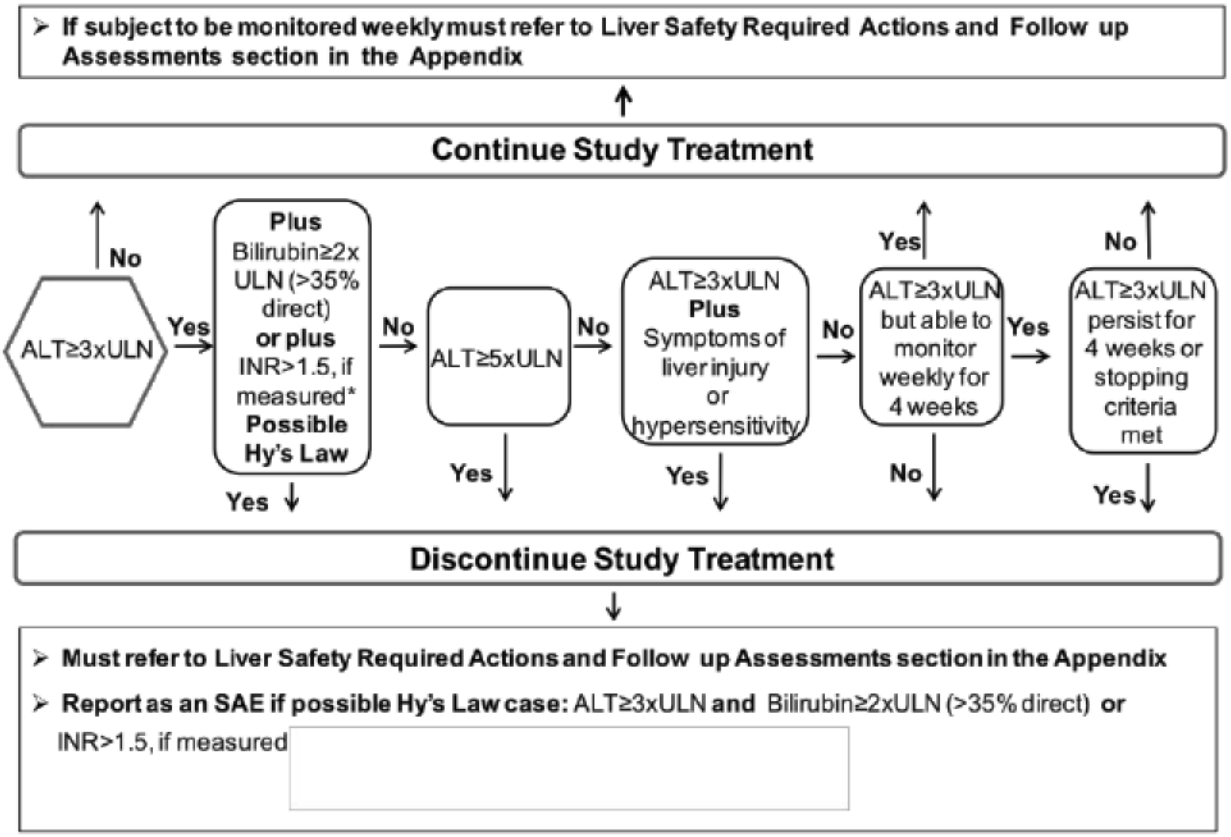
8.3 Discontinuation of the Study Medication

Study medication will be discontinued for a subject if the subject meets any stopping criteria described in this section.

8.3.1 Liver Chemistry Stopping Criteria

Liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology and are described in Figure 8-1. Study medication will be discontinued for a subject if liver chemistry stopping criteria are met. Suggested actions and follow-up assessments can be found in Section 12.7 (Appendix 7).

Figure 8-1. Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



8.3.2 QTc Stopping Criteria

Study medication will be discontinued for a subject if QTc stopping criteria are met:

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

If the QTc stopping rule is triggered, one repeat ECG should be conducted to confirm that the initial result is accurate and persistent.

8.3.3 Suicidality Stopping Criteria

At each visit, the C-SSRS will we administered by an approved and qualified individual(s) at each site.

If a subject provides a positive answer to question 3, 4, or 5 of the C-SSRS (on suicidal ideation) at any visit, the Investigator should immediately contact the Medical Monitor and discuss possible termination of the subject's participation in the study, as well as appropriate safety follow-up steps.

In addition, a response of "2" or "3" to BDI item 9 should be evaluated in conjunction with the C-SSRS and discussed with the Medical Monitor, and appropriate safety steps taken (which may include termination from the study), as needed.

8.3.4 Adrenal Insufficiency Stopping Criteria

Subjects who exhibit clinically significant signs of acute adrenal insufficiency after the initiation of SPR001, including symptoms such as postural hypotension, nausea, and abdominal pain, should have their dose(s) of SPR001 withheld, appropriate corticosteroid therapy initiated, and the Medical Monitor contacted.

If there is no clear explanation for the subject's acute adrenal insufficiency other than the administration of SPR001, including administered doses of corticosteroid replacement and circulating levels of plasma cortisol, then the Investigator should review the subject with the Medical Monitor for potential termination from the study.

8.3.5 Depression Stopping Criteria

At each visit, subjects will complete the BDI-II. Reasons that an elevated BDI-II score might be found (aside from clinical depression) include chronic pain and stress conditions. If the BDI-II total score exceeds 29 after baseline, the Investigator should immediately contact the Medical Monitor and discuss possible termination of the subject's participation in the study, as well as appropriate safety follow-up steps.

8.3.6 Reproductive Hormone Stopping Criteria

Subjects with CAH can be expected to have abnormalities in their reproductive hormone levels, as these are key metabolic pathways directly impacted by deficiencies in the activity of the P450c21 enzyme, leading to elevated levels of precursors of cortisol. Necessary therapy with glucocorticoid and mineralocorticoid replacement treatment typically does not fully normalize adrenal steroid production pathways and signaling systems, including ACTH and CRF levels.

The consequence of these complex interactions is that subjects with CAH can be expected to have abnormal plasma concentrations of various androgens and progestogens at baseline. Therapy with an effective CRF antagonist may in fact shift the balance between various intermediates in the steroid biosynthetic pathway.

Whether these change(s) from baseline (including, but not limited to, significant changes in LH, FSH, estradiol, progesterone, or prolactin; testicular dysfunction in men; or changes in menstrual cyclicity in women) represent clinically significant reproductive abnormalities will also be a reason to contact the Medical Monitor and discuss potential risks to the subject and possible termination of the subject's participation in the study, as well as appropriate safety follow-up steps.

8.4 Withdrawal from the Study

Subjects may voluntarily withdraw from the study or be withdrawn by the Investigator at any time. Subjects who become pregnant while participating in the study must be withdrawn from the study, though follow-up information about the participant and the neonate may be collected (see Section 12.5.2.2).

If a subject withdraws or is withdrawn from the study, or if the subject fails to return for visits, the Investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information on the End of Treatment case report form. Subjects may be withdrawn from the study prematurely for any of the following reasons:

- AE(s)
- Noncompliance with study procedures/restrictions
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Study terminated by Spruce Biosciences ("Spruce")
- Desire or need to start new therapy contraindicated by this protocol
- Desire or need to start new therapy for CAH

8.5 Loss to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

9 STUDY ASSESSMENTS AND PROCEDURES

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study medication. Adherence to the study design requirements, including those specified in the Schedules of Assessments, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

9.1 Efficacy Assessments

9.1.1 Pharmacokinetics and Pharmacodynamics

Blood samples will be collected for PK measurements of concentrations of SPR001 and PD measurements of 17-OHP, ACTH, androstenedione, testosterone, and glucocorticoids, as specified in the Schedules of Assessments.

In Cohort A, serial blood collections will be made for baseline PD measurements only during the overnight visit that starts on Day -1 and for both PK/PD measurements during the overnight visits that start on Days 0, 13, 27, and 41. The first timepoint for serial blood sampling will be immediately pre-dose (or, for baseline PD, at 10p on Day -1). Subsequent timepoints will be at 4, 5, 6, 8, and 10 hours thereafter.

In Cohorts B/C/D, serial blood samples will be drawn for baseline PD measurements only at the baseline visit and for both PK/PD measurements at the end of the 2-week treatment period. The first timepoint for serial blood sampling will be immediately before the AM dose (or, for baseline PD, at the time the AM dose of study drug would be). Subsequent timepoints will be at 2, 3, 4, 5, 6, 7, and 8 hours after the time corresponding to the AM dose, then every 2 hours thereafter through the time corresponding to the PM dose, and at 4, 5, 6, and 8 hours after the time corresponding to the PM dose, then every 2 hours thereafter through the time corresponding to the next AM dose. Thus, for Cohorts B and C, in which study drug will be administered at 10a and 10p, serial blood samples will be drawn at 10a (or immediately pre-dose), 12p, 1p, 2p, 3p, 4p, 5p, 6p, 8p, 10p (or immediately pre-dose), 2a, 3a, 4a, 6a, 8a, and 10a (or immediately pre-dose). A single blood sample will also be drawn for PK/PD measurements at approximately 10a during the Day 8 and safety follow-up outpatient visits. In Cohort D, the number of blood samples for PK/PD measurements will not be increased, but their timing may be adjusted based on changes to the dosing regimen and available PK/PD data from prior cohorts. The actual date and time (24-hour clock time) of each sample collection will be recorded.

In Cohorts B/C/D, 24-hour urine samples will be collected to measure urine 17-OHP and free cortisol, as specified in the Schedule of Assessments for Cohorts B/C/D. Urine concentrations of SPR001 and exploratory urine biomarkers may also be measured. 24-hour urine will be collected during each inpatient visit in 2 aliquots: the first aliquot from the time corresponding to the AM dose to immediately before the time corresponding to the PM dose, the second aliquot from the time corresponding to the PM dose to immediately before the time corresponding to the subsequent AM dose. Thus, for Cohorts B and C, in which study drug will be administered at 10a and 10p, the first aliquot of 24-hour urine will be collected from 10a to 10p, and the second aliquot will be collected from 10p to 10a the following morning.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. Separate tubes will be collected for plasma and serum, and each sample will be divided into aliquots for appropriate assessments and backup. Samples collected for analyses of SPR001 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Additional blood samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The Institutional Review Board (IRB) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).

9.1.2 Congenital Adrenal Hyperplasia Signs and Symptoms Interview

Subjects will be asked about the following signs and symptoms:

- General health status
- Fatigue
- Activity changes
- Changes in concentration
- Sleep problems
- Appetite changes
- Mood changes
- Dizziness
- Sweating
- Fluid retention
- Acne
- Headaches
- Nausea
- Joint/muscle aches
- Back pain
- Weakness
- Moon facies

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

9.1.3 Short Form 36

The Short Form 36 (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. The SF-36 can be used either as an acute measurement that asks subjects to complete the questions in response to how they have felt in the last week or as a longer-term measurement that asks subjects to complete the questions in response to how they have felt in the last 4 weeks. The acute SF-36 will be used in this study.

9.1.4 Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) (Guy, 1976) is a 1-question survey that evaluates whether there has been an improvement in overall subjective health status. Subjects select a response on a 7-point Likert scale.

9.2 Safety Assessments

Planned time points for all safety assessments are provided in the Schedules of Assessments, Section 2.

9.2.1 Physical Examinations

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 physical examination may exclude rectal, genitourinary (female subjects), and breast examinations. Male subjects should have a testicular exam as part of the physical examinations.

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

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

As part of the full and abbreviated physical exam, women should be asked about the date, duration, and nature of their last menstrual period.

9.2.2 Vital Signs

Body temperature, pulse rate, and supine blood pressure will be measured as specified in the Schedules of Assessments and as clinically indicated.

9.2.3 Body Weight and Height

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 will be recorded at Screening (Visit 1).

Body mass index (BMI) will be calculated for every visit using height and weight measurements.

9.2.4 Electrocardiogram

12-lead ECGs will be obtained as outlined in the Schedules of Assessments using an ECG machine that automatically calculates the heart rate, QRS, QT, and QTc intervals, preferably by Fridericia's formula. Refer to Section 8.3.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary. If the QTc stopping rule is triggered, 1 repeat ECG should be conducted to confirm that the initial result is accurate and persistent.

9.2.5 Testicular Ultrasound

Testicular ultrasounds for male subjects will be performed as outlined in the Schedules of Assessments.

9.2.6 Clinical Safety Laboratory Assessment

See Section 12.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the Schedules of Assessments for the timing and frequency.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study medication should be repeated 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.

All protocol-required laboratory assessments, as defined in Section 12.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the Schedules of Assessments.

9.2.7 Screening Psychiatric Evaluation

The M.I.N.I. (Version 7.0.2) is a structured clinical interview consistent with the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Health Disorders - Fifth Edition (DSM-V). The M.I.N.I. is to be administered by a trained and qualified clinician at each site and will be conducted at screening to identify subjects with the following exclusionary psychiatric comorbidities:

- Current Major Depressive Episode
- Bipolar Disorder (any type; lifetime)
- Schizophrenia
- Schizoaffective Disorder
- Major Depressive Disorder (MDD) with psychotic features
- Any other psychotic disorder

9.2.8 Monitoring for Depression and Anxiety

The BDI-II is a 21-item self-reported rating inventory measuring characteristic attitudes and symptoms of depression that is in line with the depression criteria of the DSM-V. The BDI-II will be completed by the subject at each visit; a total score >29 will require discussion with the Medical Monitor to assess whether the increased score is indicative of clinically significant depression.

The HADS (Zigmond and Snaith, 1983) is a widely used, relatively simple, validated, patient-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 to 3, with higher scores corresponding to more severe anxiety or depression. Thus, the maximum score for each subscale is 21. In general for each subscale, scores of 0 to 7 are considered normal, scores of 8 to 10 borderline, and scores of ≥11 clinically abnormal.

See Section 8.3.5 for depression stopping criteria.

9.2.9 Suicidal Risk Monitoring

Baseline and treatment-emergent suicidal ideation and behavior will be assessed during the study using the C-SSRS, which will be administered at each in-clinic visit.

SPR001 is considered to be a central nervous system (CNS)–active study medication. There has been some concern that some CNS-active study medications may be associated with an increased risk of suicidal ideation in certain populations. Although this study medication 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 clinical study.

Participants being treated with SPR001 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing SPR001 in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants being treated with SPR001 should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator. See Section 8.3.3 for suicidality stopping criteria.

9.3 Adverse Events

All observed or volunteered AEs, regardless of suspected causal relationship to the investigational product, will be recorded from screening (after the ICF is signed) until 30 days after the last day of dosing and reported as described in the following sections.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (Section 9.3.3), requiring immediate notification to Spruce or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to assess the causality of the AE. The Investigator is required to assess causality. For AEs with a suspected causal relationship to the investigational product, follow-up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator and Spruce concurs with that assessment.

9.3.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

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

9.3.1.1 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- 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.

9.3.1.2 Procedures

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.

9.3.2 Treatment-Emergent Adverse Events

An event that is temporally associated with administration of study product is defined as a treatment-emergent adverse event (TEAE). Events meeting this definition will be those occurring 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 occurring on the date of the first dose of study drug, the time of onset (before or after the intake of study drug) must be specified.

9.3.3 Serious Adverse Events

An SAE or serious adverse drug reaction (ADR) is any untoward medical occurrence at any dose that:

- 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
- Results in congenital anomaly/birth defect
- Is an important medical event

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events 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 (eg, 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:

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

9.3.4 Adverse Events of Special Interest

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

- Suicidality as indicated by type 3 or higher ideation on the C-SSRS. This should be reported as an AE of special interest until it becomes serious according to the SAE definition (eg hospitalization).
- High BDI scores or other indications of worsening depression and/or "changes in behavior."
- Significant LFT changes that do not satisfy stopping rules (Section 12.7 [Appendix 7]). Cases of Hy's Law should be reported as an SAE.
- DLTs

9.3.5 Disease-Related Events

The following disease-related events (DREs) are common in participants 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
- Hirsutism and voice virilization
- 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
- Menstrual irregularities
- Myopathies
- Obesity
- Psychiatric disorders, substance use disorders, mood swings, challenges with social interactions
- Seizures have been reported during episodes of hyponatremia and of hypoglycemia
- TART
- Weakness / lethargy / fatigue

9.3.6 Pregnancy

Any subject who becomes pregnant during the study should have study drug discontinued immediately and be terminated from the study. All pregnancies in female subjects or in the female partners of male subjects must be reported to the Sponsor or designee as outlined in Section 12.5.2 (Appendix 5) within 24 hours of the site's awareness.

9.3.7 Severity Assessment

The severity of each AE will be determined using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, summarized in Table 9-1.

Table 9-1. Severity Assessment of Adverse Events

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

Abbreviations: ADL = activities of daily living; AE = adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. 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 9.3.3.

9.3.8 Causality Assessment

The Investigator's assessment of causality must be provided for all AEs, both serious and non-serious. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to the AE. Five different causality designations are available, ranging from "unrelated" to "definitely related," as defined in Table 9-2. The Investigator should utilize these definitions when assessing the causality of each AE.

Table 9-2. Relationship between Investigational Product and Adverse Events

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 after 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 the administration of study drug 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 after 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 after administration of the study drug; (2) it cannot not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject; (3) it disappears or decreases on cessation or reduction in dose of study drug. There are exceptions when an AE does not disappear upon discontinuation of the study drug yet drug-relatedness clearly exists (eg, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the study drug.
DEFINITELY RELATED: This category applies to those AEs that the Investigator thinks are incontrovertibly related to the study drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence after administration of the study drug; (2) it cannot 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 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.

9.3.9 Dose-Limiting Toxicity

A DLT is defined as a Grade 3 (severe or medically significant but not immediately life threatening) or higher AE (according to the CTCAE version 4.03, which will be provided to each site for reference purposes) considered at least possibly related to study drug. If a Grade 3 or worse event is clearly a non–treatment-related event and therefore not a suspected adverse reaction [21CFR312.32(a)] (for example, trauma secondary to an accident, or spurious lab value not confirmed on repeat), the event will not be considered a DLT for dose escalation purposes, after review and agreement by both the Sponsor's Medical Monitor and Principal Investigator.

9.3.10 Clinically Significant Adverse Events

Clinically significant AEs include but are not limited to DLTs (Section 9.3.9), SAEs (Section 9.3.3), AEs leading to study drug discontinuation, and AEs of special interest (Section 9.3.4) that are each considered at least possibly related to study drug. Also refer to Section 12.4 (Appendix 4) for AEs that may be considered clinically significant. The occurrence of any clinically significant AE will receive special consideration in decisions regarding continuation or suspension of dosing, cohort expansion, and dose selection for the next cohort and will be reported to the SRC within 1 day of awareness for immediate review.

9.3.11 Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the subject. In addition, subjects should be queried about AEs at each study visit.

9.3.12 Withdrawal Due to Adverse Events

Withdrawal due to an AE or SAE should be recorded on the appropriate AE case report form page and reported in accordance with the reporting requirements defined below.

9.3.13 Follow-up of AEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.5).

9.4 Regulatory Reporting Requirements

9.4.1 Notification to the Sponsor of Events Requiring Immediate Reporting

Throughout the study, all SAEs, all AEs leading to permanent discontinuation of study medication, and cases of pregnancy, regardless of suspected causality, must be reported to Spruce within 24 hours of learning of its occurrence. Any SAEs experienced after the 30-day follow-up period should only be reported to Spruce if the Investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE 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 one should be reported separately as a new event.

Information about SAEs and other AEs of special interest will be recorded on the SAE Report Form; information on pregnancies will be recorded on the Pregnancy Report Form. SAEs must be clearly differentiated from other types of events through the usage of the SAE Report Form. The Investigator must assess and record the relationship of each event to the study drug and complete the SAE Report Form in English. SAEs must also be captured in the case report form.

Follow-up information should be provided following the procedures pre-defined for the study, indicating that the information is follow-up to a previously reported SAE. Each recurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation. The SAE Report Form and completion guidelines are found in the Investigator Site File.

Forms should be sent to the Sponsor via fax or email using the contact information provided on the SAE form.

9.4.2 Non-Serious Adverse Event Reporting

Non-serious AEs that don't require immediate reporting are to be reported on the AE case report form. AEs that occur in the time period between informed consent and administration of trial drug should be recorded but will not be considered TEAEs. If the AE occurs on the date of first

dose, the time of onset will be captured to determine if the AE occurred before or after study drug.

9.5 Exploratory Work

9.5.1 Metabolite Identification

Plasma remaining following PK and PD evaluation may be banked and used for metabolite identification studies as deemed appropriate.

9.5.2 Genetics

For participants who consent to participate in the genetic testing, any available prior genetic screening results should be provided to the site for inclusion in the database or a blood sample for deoxyribonucleic acid (DNA) isolation will be collected. Participants who do not wish to participate in the genetic research may still participate in the study if they have a confirmed medical diagnosis of classic CAH.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

See Section 12.6 (Appendix 6) for information regarding genetic research.

9.5.3 Salivary 17-OHP

Saliva samples will be obtained at all visits to evaluate the potential utility of this non-invasive sampling technique for future studies.

9.5.4 Exploratory Biomarkers

In Cohorts B/C/D, a separate blood sample will be drawn at approximately 10a at each visit specified in the Schedule of Assessments and stored for measurement of exploratory biomarkers.

Urine concentrations of SPR001 and exploratory urine biomarkers may also be measured from the 24-hour urine samples collected.

10 STATISTICAL METHODS AND DATA ANALYSIS

A detailed SAP will be developed. Unless otherwise specified, statistical analyses will be performed using SAS Version 9 or higher.

10.1 Populations for Analysis

The Full Analysis Set (FAS)/Safety Population consists of all enrolled subjects who received at least 1 dose of study drug.

The Per Protocol Population consists of all subjects who received at least 80% of study drug administrations and had no major protocol violations. The Per Protocol Population will be identified prior to database lock.

10.2 Subject Demographics / Other Baseline Characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively overall, for each dose level, and by cohort. Categorical data will be presented as

frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

10.3 Subject Disposition

Data regarding subject disposition in the trial, including the number of screen failures, early withdrawals, dose escalations, down-titrations, and the number of subjects in each completed cohort, will be summarized descriptively.

10.4 Compliance

Descriptive statistics will be used to summarize the mean daily dose and total dose of study medication for each dose level, by cohort, and overall. The actual and planned doses administered and reason for dose change will be listed.

These analyses will be performed on the Safety Population.

10.5 Pharmacokinetic Analyses

10.5.1 Pharmacokinetic Parameter Estimation

PK parameter estimates for SPR001 will be calculated by a standard noncompartmental method of analysis and, where appropriate, by compartmental method of analysis. The primary parameter for analysis will be AUC.

As an exploratory assessment of drug-drug interactions with exogenously administered glucocorticoids, the primary parameter for analysis will be AUC of glucocorticoids. Other noncompartmental parameters may be reported as data permit.

10.5.2 Pharmacokinetic Statistical Inference

An assessment of dose proportionality of SPR001 observed in this study will be investigated with the power model approach. The dose-normalized ratio of geometric means and its 90% confidence intervals between the highest and lowest dose tested will be calculated and presented. Coefficients of variation (intra- and inter-subject) may also be reported. Accumulation of SPR001 at approximate steady state (after 2 weeks of dosing) will be assessed by 1 or more approaches, including but not restricted to accumulation ratio. Additional analyses may be performed if warranted upon review of the data.

10.6 Pharmacodynamic Analyses

Inferences will be sought regarding the ability of SPR001 to attenuate the early morning rise in 17-OHP and ACTH and to attenuate accumulation of androstenedione and testosterone. The effects of SPR001 on PD measures will be explored over a range of doses.

10.6.1 Pharmacodynamic Parameter Estimation

PD parameter estimates for 17-OHP, ACTH, androstenedione, and testosterone will be determined by noncompartmental analysis using serum/plasma concentrations. The primary parameters for analysis will be AUC for 17-OHP and ACTH based on measurements during overnight PK/PD assessment. AUC will be calculated using the linear trapezoidal method.

10.6.2 Pharmacodynamic Statistical Inference

Hormone levels will be summarized by descriptive statistics for each dose level. Parametric (paired t test) and nonparametric (Wilcoxon signed rank) tests will be used to test the change from baseline depending on the data distribution. Additional analyses on diurnal rhythm may be performed if warranted upon review of the data.

Other statistical comparisons may be conducted as appropriate.

10.7 Pharmacokinetic/Pharmacodynamic Analyses

The relationship of 17-OHP, ACTH, androstenedione, and testosterone to SPR001 will be explored by SPR001 exposure, duration of treatment, and dose level.

Other exploratory analyses may be undertaken if deemed appropriate, although the sizing of the study may not be sufficient to construct a PK/PD model.

Other statistical comparisons may be conducted as appropriate.

10.8 Patient-Reported Outcomes Analyses

Data for the SF-36 (individual domain scores and summary scores) and HADS (anxiety subscale and depression subscale) will be summarized using descriptive statistics and presented by SPR001 dose level and time point. Data for the CAH signs and symptoms interview and PGIC will be summarized using counts and percentages for each SPR001 dose level. Other statistical comparisons may be conducted as appropriate.

10.9 Safety Analyses

The safety analyses will be performed on the Safety Population. All TEAEs and AEs leading to study withdrawal will be listed by subject. Safety data will be summarized using descriptive statistics where the frequency of events allows. AEs will be coded by System Organ Class and Preferred Term according to Medical Dictionary for Regulatory Activities (MedDRA) terminology. AEs that occur before the first dose of study drug will be distinguished from TEAEs. TEAEs will be summarized overall and by dose level. The incidence of TEAEs for each dose level will be presented by severity and by Investigator-assessed relationship to study drug. All treatment-emergent AEs/SAEs considered related to study drug will be summarized. AEs of special interest and DREs will be specified in the SAP and summarized. The frequency (number and percentage) of subjects with ≥1 TEAE will be summarized by dose level. The incidence of AEs leading to study withdrawal will be tabulated.

Other safety parameters that will be assessed include safety lab parameters, vital signs, and ECG parameters. These parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.10 Review for Flexible Dosing

Data may be analyzed while the trial is ongoing. If a PK review reveals unexpected exposure predictions, dose escalation or de-escalation may occur to ensure an adequate margin of safety is maintained relative to the maximum AUC of 100,000 ng·h/mL over a 24-hour interval. If required, the PK and/or safety sampling schedule may be revised accordingly.

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.

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.

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.

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.

Esteban NV, Loughlin T, Yergey AL, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab.* 1991;72(1):39-45.

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:E2715-2721.

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

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

Kerrigan JR, Veldhuis JD, Leyo SA, Iranmanesh A, Rogol AD. Estimation of daily cortisol production and clearance rates in normal pubertal males by deconvolution analysis. *J Clin Endocrinol Metab.* 1993;76(6):1505-1510.

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.

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

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

12 APPENDICES

12.1 Appendix 1: Abbreviations

17-OHP	17-hydroxyprogesterone
ACTH	adrenocorticotropin hormone, corticotropin
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
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
C-SSRS	Columbia-Suicide Severity Rating Scale
CAH	congenital adrenal hyperplasia
cAMP	cyclic adenosine monophosphate
C_{avg}	average concentration
CFR	Code of Federal Regulations
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
CSE	clinically significant adverse effect
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

DRE	disease-related event
DSM-V	Diagnostic and Statistical Manual of Mental Health Disorders - Fifth Edition
E2	estradiol
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
hCG	human chorionic gonadotropin
HDPE	high-density polyethylene
HEENT	head, eyes, ears, neck, and throat
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board
LFT	liver function test
LH	luteinizing hormone
MAD	multiple ascending dose
M.I.N.I.	Mini International Neuropsychiatric Interview
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
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
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
$T_{1/2}$	half life
TART	testicular adrenal rest tumors
TEAE	treatment-emergent adverse event
T_{max}	time of maximum concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman of childbearing potential

12.2 Appendix 2: Clinical Laboratory Tests

Table 12-1. Protocol-Required Safety Laboratory Assessments

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, nonfasting	BUN
	Potassium	Total protein
	Calcium	Creatinine
	Sodium	Total and direct bilirubin
	Alkaline phosphatase	
	AST/ SGOT	
	ALT/ SGPT	
Routine Urinalysis	Specific gravity	
	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, by dipstick	
	Microscopic examination (if blood or protein is abnormal)	
	In-clinic urine pregnancy testing will be conducted at all visits other than the screening visit.	
Other Tests	Plasma renin activity, aldosterone, TSH, T3, T4, LH, FSH, SHBG, inhibin B; females only: E2, prolactin, progesterone	
Other Screening Tests	hCG pregnancy test (as needed for women of childbearing potential)[2]	
	All study-required laboratory assessments will be performed by a central laboratory.	

Abbreviations: ALT = alanine aminotransferase; AST aspartate aminotransferase; BUN = blood urea nitrogen; E2 = estradiol; FSH = follicle-stimulating hormone; hCG = Human chorionic gonadotropin; INR = international normalized ratio; 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 12.7 (Appendix 7). 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.

[2] Local urine testing will be standard for the protocol unless serum testing is required by the investigational site.

12.3 Appendix 3: Study Governance Considerations

12.3.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, applicable local regulations (including European Directive 2001/20/EC and CFR Title 21), and the ethical principles laid down in the Declaration of Helsinki.

12.3.2 Responsibilities of the Investigator and IRB

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB must be given to Spruce before study initiation. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Spruce's monitors, auditors, clinical quality assurance representatives, designated agents of Spruce, IRBs, and regulatory authorities as required.

12.3.3 Informed Consent

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. 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 Spruce before submission to the IRB, and a copy of the approved version must be provided to the study monitor after IRB approval.

12.3.1 Site Monitoring and Protocol Adherence

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Spruce representative will review the protocol and case report forms 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 case report forms, 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.

For each subject in the study, the Investigator must maintain source documents consisting of case and visit notes (hospital or clinic medical records) that contain demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on case report forms must be traceable to these source documents in the subject's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the case report forms, which will be documented as being the source data.

The Investigator must also keep the original ICF signed by the subject (a signed copy is given to the subject).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the case report form entries. Spruce monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the 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 the subjects will be disclosed.

Representatives of Spruce 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 Spruce 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 Spruce promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Spruce.

12.3.2 Data

12.3.2.1 Data Protection

All measures will be taken to comply with the applicable rules on protection of personal data and what to do in case of a data security breach.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

12.3.2.2 Disclosure of Data

All information obtained during the conduct of this study will be regarded as confidential, and written permission from Spruce is required prior to disclosing any information related to this study. Manuscripts for publication will be prepared in accordance with the Spruce publication policy. Submission of manuscripts to the Sponsor for review and comment is required prior to 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 to share with the Investigator any new or unpublished information of which the Investigator may be unaware.

12.3.2.3 Case Report Forms / Electronic Data Records

As used in this protocol, the term case report form should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial.

A case report form is required and should be completed for each included subject. The completed original case report forms are the sole property of Spruce and should not be made

available in any form to third parties, except for authorized representatives of Spruce or appropriate regulatory authorities, without written permission from Spruce.

It is the Investigator's responsibility to ensure completion of and to review and approve all case report forms. 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 case report forms 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 case report forms. Subject source documents are the physician's subject records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the case report forms must match those charts.

In some cases, the case report form may also serve as the source document. In these cases, Spruce and the Investigator must prospectively document which items will be recorded in the source documents and which items will be recorded in the case report form as the source document.

12.3.2.4 Record Retention

To enable evaluations and/or audits from regulatory authorities or Spruce or its designees, the Investigator agrees to keep records that include the identity of all subjects (sufficient information to link records [eg, case report forms and hospital records]), all original signed ICFs, copies of all case report forms, SAE forms, source documents, and treatment disposition. The records should be retained by the Investigator according to ICH or local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

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

12.3.3 Amendments

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, Spruce. The Investigator should not implement any deviation or change to the protocol without prior review by and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval/favorable opinion, the deviation or change will be submitted as soon as possible to:

- IRB for review and approval/favorable opinion
- Spruce
- 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 Spruce.

If the revision is an Administrative Letter, Investigators must inform their IRB(s).

If an 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 form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

12.3.4 Sponsor Discontinuation

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB, drug safety problems, or at the discretion of Spruce. In addition, Spruce retains the right to discontinue development of SPR001 at any time.

If a trial is prematurely terminated or discontinued, Spruce will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects within 7 days and have participating subjects complete final visit safety assessments. As directed by Spruce, all trial materials must be collected and all case report forms completed to the greatest extent possible.

12.4 Appendix 4: Criteria for Clinically Significant Adverse Events

This table summarizes the type and severity of symptoms, clinical signs, and clinical laboratory findings that may qualify as a clinically significant adverse effect (CSE). These are intended as guidelines to the Investigator(s), not as a set of absolute criteria.

The underlying principle is to define a level of moderate-severe abnormality in safety findings that could cause harm to health and would preclude further dosing of a subject who experiences this effect. Safety parameters not included in this table may be interpreted in a similar fashion according to Investigator judgment.

The CTCAE should also be referenced to aid in the determination of appropriate terminology and severity ratings for AEs that occur during the study.

Table 12-2. Criteria for Clinically Significant Adverse Effects - Clinical Symptoms

Event	Description
Abdominal Pain	Pain and abdominal tenderness to palpation that significantly impairs ambulation, food intake and activities of daily living (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 >3hr, 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 (for example, 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 two doses of non-steroidal analgesics.
Pruritis	Generalized itching over >24 hours unresponsive to oral antihistamine.
Systolic Blood Pressure	>30 mmHg increase from baseline values and an absolute level >180 mmHg.
Diastolic Blood Pressure	>20 mmHg increase from baseline values and 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.
QTcF	>500 msec or >60 msec increase from baseline value
QRS Morphology	Significant prolongation of QRS interval or new onset of bundle branch block.
Skin Rash	Pruritic rash or urticaria over >100 cm^2 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

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

Table 12-3. Criteria for Potentially Clinically Significant Adverse Effects - Clinical Laboratories

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
Creatinine	>1.8 mg/dL and >0.4 mg/dL increase from baseline value
Blood urea nitrogen	>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; FSH = follicle-stimulating hormone.
Note: If a laboratory result meets any of these criteria, it should be confirmed by repeat measurement within 48 hours.

12.5 Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

12.5.1 Contraceptive Guidance

12.5.1.1 Male Participants

Males with female partners of childbearing potential, including those who are breastfeeding, are eligible to participate if they agree to ONE of the following:

1. Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
2. Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 12-4 for the duration of the study.
3. Agree to refrain from donating sperm throughout the treatment period and for 90 days after the last dose of study medication.

12.5.1.2 Female Participants

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Women in the following categories are not considered women of childbearing potential (WOCBP):

1. Premenarchal
2. Premenopausal female with one of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy
3. Postmenopausal
    a. A postmenopausal state is defined as no menses for 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 (HRT). However, in the absence of 1 year of amenorrhea, a single FSH measurement is insufficient.

Females are eligible to participate if they are either not considered WOCBP or agree to use a highly effective contraceptive method (described in Table 12-4) for the duration of the study.

Table 12-4. Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

Abbreviations: IUD = intrauterine device; IUS = intrauterine hormone-releasing system; WOCBP = woman of childbearing potential.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study medication, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study medication.

12.5.2 Collection of Pregnancy Information

12.5.2.1 Male Participants with Partners Who Become Pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive at least 1 dose of SPR001.

The Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following 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.

12.5.2.2 Female Participants Who Become Pregnant

The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of the site learning of the pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. An elective termination of a pregnancy is not considered an SAE. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

12.6 Appendix 6: Genetics

Genetic testing and storage of identifiable samples (eg, with subject identifier numbers) for pharmacogenomics evaluation is an optional part of this study. This sample may be tested for drug metabolism enzyme and transporter polymorphisms. These polymorphisms may be evaluated using an analytical methodology that comprehensively assesses an array of drug metabolism enzyme and transporter genes from a single sample. Additionally, genes related to the mechanism of action of SPR001 may be evaluated. Alternative genotyping platforms may be used, if appropriate, to confirm initial results. Subjects may have the genotyping omitted at the discretion of the Investigator and/or Sponsor (eg, if previously tested using the same platform/technology). Samples will be stored for a maximum of 5 years after the last subject visit for the study; any sample remaining at that time will be destroyed. Samples will be stored at a facility selected by the study Sponsor.

12.7 Appendix 7: Liver Safety

Liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Figure 12-1. Liver Chemistry Stopping Criteria and Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥5x ULN
ALT Increase	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 medication. • Report the event to the Sponsor or designated CRO within 24 hours. • Complete the liver event case report form, 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 medication 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>**	• 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 according to standard overnight assessment schedule 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 case report form. • Record alcohol use on the liver event case

• Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, and bilirubin) and perform liver event follow-up assessments within **24 hours**. • Monitor participant 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 participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	report form. **<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 antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury) in participants 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 medication 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 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 medication prior to the blood sample draw on the case report form. If the date or time of the last dose is unclear, provide the participant'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.

Figure 12-2. Liver Chemistry Increased Monitoring Criteria with Continued Therapy

Liver Chemistry Increased Monitoring Criterion and Follow-up	
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 participant safety. • Participant can continue study medication. • Participant 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 participant meets liver chemistry stopping criteria, proceed as described in Section 8.3.1. • 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.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate transaminase; ULN = upper limit of normal.

12.7.1 Restart Following Transient Resolving Liver Chemistry Events Not Related to Study Medication

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 medication restart can be considered when:

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

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

- Study medication must be administered at the dose specified by the Sponsor.

- Participants approved by the Sponsor for restart of study medication 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 participant meets protocol-defined liver chemistry stopping criteria after study medication restart, study medication should be permanently discontinued.
- The Medical Monitor must be informed of the outcome for the participant following study medication restart.
- The Sponsor must be notified of any AEs.

12.8 Appendix 8: Excluded Concomitant Medications and Other Medications of Concern

Rosiglitazone treatment is not permitted during the study as it could affect the subject's ACTH levels. Treatment with testosterone is also prohibited.

Drugs that are known to be potent inducers or inhibitors of CYP3A4 are generally excluded because of their potential impact on the metabolism of SPR001. For any questions, the Investigator should consult with the Medical Monitor before enrolling the subject in the study. Stable daily doses of glucocorticoids and birth control are not restricted.

Table 12-5. Excluded CYP3A4 Inhibitors and Inducers[1]

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

[1]Many medications used to treat human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are strong inhibitors of CYP3A4 but are not listed above since subjects with HIV and/or HCV are excluded.

Drugs that are considered sensitive substrates[1] or substrates with narrow therapeutic ranges[2] for CYP3A4, CYP2C8, CYP 2C9, and/or CYP2C19 should be avoided as much as possible. Whenever feasible, the subject will discontinue use of the "medication of concern." As with the excluded metabolic inhibitors and inducers, ideally there will be 30 days or 5 half-lives between the last dose of the "medication of concern" and the first dose of study drug. However, if washout is not feasible, then the Investigator should consult the Medical Monitor to jointly decide on the best course of action. If a medication on the list below is to be continued, it must be used with caution and the subject carefully followed.

Table 12-6. Medications of Concern: Sensitive Substrates and Substrates with Narrow Therapeutic Windows (Metabolized by CYP3A4, 2C8, 2C9, or 2C19)[1,2]

Alfentanil	Lovastatin
Aprepitant	Lurasidone
Avanafil[3]	Midazolam
Budesonide	Nalogexol
Buspirone	Nisoldipine
Capsaicin	Omeprazole
Celexocib	Pimozide
Clobazam	Quetiapine
Darifenacin	Quinidine
Dihydroergotamine	Repaglanide
Dronedarone	Sildenafil[3]
Eletriptan	Simvastatin
Eplerenone	Tacrolimus
Ergotamine	Ticagrelor
Felodipine	Tolvaptan
Fentanyl	Triazolam
Fluticasone	Vardenafil[3]
Lansoprazole	Warfarin
Lomitapide	

[1] *Sensitive CYP substrates* refers to drugs whose plasma area under the concentration-time curve (AUC) values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor or whose AUC ratio in poor metabolizers vs extensive metabolizers is greater than 5-fold.

[2] *CYP substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, torsades de pointes).

[3] Subject must be willing to refrain from use of PDE-5 inhibitors during study.