NCT03687242

STATISTICAL ANALYSIS PLAN
PHASE II

VERSION: 2.0

DATE OF PLAN:

April 20, 2020

BASED ON:

Protocol Version 1.0: 24 May 2018

STUDY DRUG:

TILDACERFONT (SPR001)

PROTOCOL NUMBER:

202

STUDY TITLE:

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

SPONSOR:

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

SAP Phase II

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

Plan Version: 2.0

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Reviewer:

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Spruce Biosciences, Inc.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
17-OHP	17-hydroxyprogesterone
A4	Androstenedione
ACTH	Adrenocorticotropin hormone, corticotropin
AE	Adverse Event
C	Continuous reporting format
CAH	Congenital adrenal hyperplasia
CRF	Case Report Form
CSR	Clinical Study Report
dy	Days
F	Frequency reporting format
G	Geometric mean reporting format
GCP	Good Clinical Practices
HbA1c	hemoglobin A1c
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MF	Multiple frequency reporting format
mITT	Modified Intent-to-Treat
mo	Months
N	Total Sample Size
OTC	Over the Counter Medication
PP	Per-Protocol Population
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SF-36	Short Form 36
TART	Testicular adrenal rest tumor
ULN	Upper Limit of Normal
WHO	World Health Organization
yr	Years

2. INTRODUCTION

This document outlines the initial plan for the summarization and analysis of clinical data collected in Study SPR001-202 for tildacerfont, SPR001.

The analysis of pharmacokinetics (data derivation and summary of individual PK parameters) is outside the scope of this document and is not addressed here.

This document describes the a priori plan for analysis. Once the analysis is in progress, it may become apparent from the data that the planned analysis should be modified. Any substantive modification to the original analysis plan will be identified in the clinical study report (CSR).

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective is:

- To evaluate the safety of SPR001 in subjects with CAH.

3.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of SPR001 in subjects with CAH in terms of changes in hormones.

3.1.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate the effect of SPR001 on quality of life (QoL), metabolic parameters, exploratory adrenal hormones, and sex-specific outcomes in subjects with CAH.

3.2. Study Endpoints

3.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Adverse events (AE) and Serious adverse events (SAE).

Additional safety endpoints include the following:

- Change from baseline in safety laboratory, vital signs, and electrocardiogram (ECG) parameters,
- Clinical changes as determined by physical examinations (including testicular ultrasound for males),
- Suicidality as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS), and
- Hospital Anxiety and Depression Scale (HADS)
- Concomitant medication usage.

3.2.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints of this study are:

- Change and percent change from baseline in plasma or serum biomarkers: 17-OHP, ACTH, androstenedione (A4), and testosterone.

3.2.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints of this study are:

- Changes in QoL as measured using the Short Form 36(SF-36),
- Changes in Patient Global Impression of Change (PGIC),
- Changes in bother score
- Changes in CAH signs and symptoms total score,
- Changes in fasting glucose,
- Changes in hemoglobin A1c (HbA1c),
- Changes in lipid profile,
- Changes in body weight (BW) and body mass index (BMI),
- Changes in acne,
- Changes in hirsutism in females subjects,
- Changes in menstrual cyclicity in female subjects,
- Changes in TARTs and on semen analysis in male subjects.

4. STUDY DESIGN

4.1. Summary of Study Design

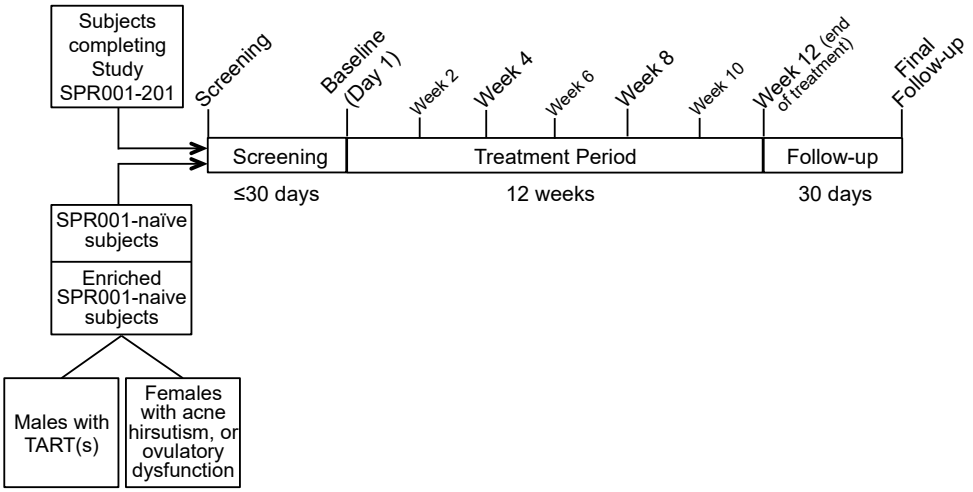
This is a Phase 2 study of SPR001 for the treatment of classic CAH that will provide 12 weeks of open-label treatment to eligible subjects. To be eligible for this study, an individual must either have completed Study SPR001-201 or meet criteria for SPR001-naïve subjects outlined under Eligibility Criteria.

Subjects who enroll in this study will be treated with SPR001 at 400 mg once a day (QD) during the treatment period.

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

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

Figure 1: Study Schema



4.2. Definition of Study Drugs

Study drug comprises the following:

- SPR001 400 mg once daily (two 200 mg capsules): Taken orally for up to 12 weeks in the evening (approximately 10 pm or bedtime) with a snack

4.3. Sample Size Considerations

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

The final sample size for the study is n=11.

4.4. Randomization

This is an open label study. All enrolled subjects receive the same treatment with no randomization.

4.5. Clinical Assessments

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

[1] For subjects rolling over from Study SPR001-201, the final safety follow-up visit of Study SPR001-201 may coincide with the screening visit of this study (with any overlapping assessments conducted only once). If a subject completed the final follow-up visit of Study SPR001-201 ≤3 months before the screening period of this study, overlapping assessments conducted at that final follow-up visit need not be repeated at screening for this study. If a subject completed the final follow-up visit of Study SPR001-201 >3 months before the screening period of this study, all screening assessments must be conducted anew, including some additional screening assessments specified for such subjects.

[2] All visits should be performed on the indicated study days. In cases where this is not possible, the following visit windows apply: ±3 days for Visits 3 to 8 and ±7 days for the safety follow-up visit (Visit 9). All visits, including the early termination visit, should be scheduled for the morning, to accommodate 8am laboratory assessments.

[3] Study visits for screening; at Weeks 0, 4, 8, and 12; and at final follow-up must be conducted as in-clinic outpatient visits.

[4] Study visits at Weeks 2, 6, and 10 may be conducted as either in-clinic outpatient visits or in-home visits by qualified study personnel.

[5] Demographic information needs to be collected only for SPR001-naïve subjects.

[6] Full medical history and prior medications from the past year will be collected for SPR001-naïve subjects. If a subject completed the final follow-up visit in Study SPR001-201 before the screening period for this study, any significant medical history and medications taken during the intervening period should be captured.

[7] Subjects should be on a stable regimen of glucocorticoid replacement for a minimum of 30 days before baseline and throughout the treatment period. On the mornings of all study visits, including screening, subjects should hold off on taking any morning glucocorticoid medication until after laboratory assessments have been completed. On all other days during the study, subjects may take any morning dose of glucocorticoid medication at their usual time.

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

[8] Samples for these lab assessments will be obtained at the beginning of each study visit (8am), after overnight fast (nothing to eat since the previous midnight), and before the subject has taken any morning dose of glucocorticoid medication. If a morning dose of study drug is added, samples for these lab assessments will be obtained before the morning dose of study drug for that day (where applicable).

[9] Clinical laboratory assessments include hematology, clinical chemistry, fasting glucose, lipid panel, thyroid panel, urinalysis, LH, FSH, inhibin B, SHBG, renin, aldosterone, and, for females only, estradiol, prolactin, and progesterone.

[10] ACTH, 17-OHP, androstenedione, testosterone, and background glucocorticoid levels (cortisol/prednisolone/dexamethasone, depending on what the subject is taking) will be measured from blood samples. 17-OHP will also be measured from a saliva sample.

[11] A single blood sample will be drawn for measurement of exploratory adrenal hormones at each specified visit.

[12] A single blood sample will be drawn for PK measurement at each specified visit. The PK blood sample does not need to be obtained from SPR001-naïve subjects at screening.

[13] These screening assessments will be performed for SPR001-naïve subjects and for subjects who completed the final follow-up visit in Study SPR001-201 >3 months before the screening visit for this study.

[14] eGFR for screening will be calculated from blood creatinine measured as part of clinical chemistry during screening.

[15] A serum pregnancy test will be performed at screening for WOCP who are SPR001-naïve and for WOCP who completed the final follow-up visit in Study SPR001-201 >3 months before the screening visit for this study. All other pregnancy tests will be urine pregnancy tests.

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

	Screening Period	Treatment Period							Follow-up/ET
VISIT NUMBER	**1[1] Screening**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
STUDY WEEK		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
STUDY DAY[2]	**≤30 days before Day 1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**Last dose +30 days**
Site Visits[3]	**X**	**X**		**X**		**X**		**X**	**X**
Home Visits[4]			**X**		**X**		**X**		
Physical examination[17]	X	X		X		X		X	X
Scrotal ultrasound for males	X[18]	X						X	
Optional semen sample for males[19]		X						X	
12-lead ECG	X	X		X		X		X	
MINI Version 7.0.2[13]	X								
C-SSRS	X	X		X		X		X	
HADS	X	X		X		X		X	X
SF-36[20]		X		X		X		X	X
PGIC				X		X		X	X
Bother score		X		X		X		X	
CAH signs and symptoms interview		X		X		X		X	X
Diary	X								
Dispense study drug[21]		X		X		X			
Study drug accountability			X	X	X	X	X	X	
Review adverse events		X	X	X	X	X	X	X	X

[17] A full physical examination will be conducted at baseline (Day 1) and end of treatment (Week 12) for all subjects. A full physical examination will also be conducted at screening for SPR001-naïve subjects and subjects who completed the final follow-up visit in Study SPR001-201 >3 months before the screening visit for this study. The full physical examination may exclude rectal, genitourinary, and breast exams. An abbreviated physical examination will be conducted at Weeks 4 and 8 and final follow-up. Height needs to be collected at screening only. As part of the examination of the skin, acne will be evaluated for all subjects using an IGA score at baseline and Weeks 4, 8, and 12; hirsutism will be evaluated for female subjects using an mFG score at baseline and Week 12. Female subjects will be asked about their last menstrual period as part of both full and abbreviated physical exams.

[18] A scrotal ultrasound is required at screening only for SPR001-naïve male subjects.

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

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

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

5. PLANNED ANALYSES

5.1.1. Changes to Protocol Specified Analyses

Due to the low enrollment numbers for subjects enriched with acne and hirsutism at baseline (n=2), these endpoints will not be summarized.

Due to no samples collected, analysis of semen will not be summarized.

Due to the study short duration and lack of adequate baseline data, menstrual cyclicality will not be summarized.

5.1.2. Revisions to Version 1.0 Statistical analysis plan

The following changes are identified between version 1.0 and version 2.0 of the SAP

Subject 004-004 was determined to be off treatment prior to the Week 4 (Day 28) visit starting at Day 21. The following pharmacodynamic assessments were conducted and for the purposes of summary analysis will bet set to missing as this is an exploratory study with the primary intent to characterize on-treatment pharmacodynamic effects during the first 12 weeks of the study.

Analysis Visit	Parameter	Value	Summary Value
Week 4	17-OHP	24746	missing
Week 4	ACTH	570.1	missing
Week 4	A4	1711	missing
Week 4	TEST	459.5	missing

5.1.3. Interim Analyses

As this study is open-label, data cuts may be taken during study conduct to inform the future development plan for tildacerfont. No formal statistical analyses are conducted in this SAP.

5.1.4. Final Analysis

The final analysis is planned once all enrolled subjects complete the Week 16 visit or discontinue prior to Week 16.

6. CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

All data from scheduled and unscheduled visits will be presented in the subject listings.

However, unless noted otherwise, only data from scheduled/windowed visits will be included in the summaries, statistical analysis, and calculation of derived parameters.

6.1. Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings (e.g., post text tables and individual subject data listings are prepared according to ICH Guideline E3) include a "footer" providing explanatory notes.

6.2. Data Management

Analyses and tabulations will generally be prepared using SAS®, version 9.3 or later.

Adverse Events

Recorded adverse events will be mapped according to the MedDRA thesaurus with Theravance review and approval of the mappings. MedDRA, version 21.0 will be used

Medications

Recorded prior and concomitant medication names will be mapped according to the World Health Organization Drug Dictionary (WHODD) for this study with Theravance review and approval of the mappings. The 3Q2108 version of the WHODD will be used.

Medical History

Medical history will be mapped according to MedDRA version 21.0 and will be provided in listings.

6.3. Data Presentation Conventions

Table, Figure and Listing titles

Table, figures and listing titles are denoted in underlined text in this SAP. For a complete list, see Appendix Section 11.3.

Reporting Formats

Appendix Section 11.1 lists the available reporting formats for summaries.

Presenting Multiple Summaries on Same Table Summary

In summary tables in which multiple single line frequency summaries are being presented, the "n line" can be suppressed in the individual summaries and presented at the top of the summary a single time.

Ordering of Treatment Headers in Summary Tables

In summary tables, treatment headers will be presented in the following order:

- Tildacerfont 400 mg QD.

Rounding

In general, the convention for rounding percentages is as follows:

- Values greater than or equal to x.x5 are rounded up,
- Values between 0 and less than x.x5 are rounded down,
- Values between –x.x5 and 0 are rounded up,
- Values less than or equal to –x.x5 are rounded down.

Significant Digits

Raw measurements will be reported the same as the data captured electronically or on the CRFs. Exceptions will be made for values reported with greater than 4 significant digits (round to 4 significant digits using a similar criterion as for percentages with the 5 in the last digit)).

The following significant digit convention will be used for the purposes of summarizing data in tables:

- Mean, median: 2 significant digits,
- Standard deviation: 3 significant digits,
- Minimum, maximum: 2 significant digits,
- Percentages: 1 decimal place.

P-values

P-values will be reported with 4 significant digits except when reporting p-values less than 0.001, reported as < 0.001. No p-values smaller than <0.001 will be reported.

Colors/Symbols in Figures

In figures that only contain the 3 treatment groups, the following colors will be used:

- SPR001 400 mg QD (dodger blue- CX1E90FF / Square filled),

6.4. Analysis Populations

6.4.1. Screen Failures

Subjects who give informed written consent but are not randomized are considered screen failures. Screen failure subjects and the main reason for screen fail will be captured in the EDC.

6.4.2. Enrolled Population

The Enrolled analysis set will include all subjects who were enrolled into the study.

6.4.3. Safety Population

The Safety analysis set will include all subjects who

1. Were enrolled into the study, and,
2. Received at least one dose of study drug.

The Safety analysis set is the primary analysis set for all analyses.

6.4.4. Per-Protocol (PP) Population

The Per-protocol analysis set included all subjects in the safety analysis set who meet the following criteria:

1. No major analysis protocol deviations

Treatment assignment will be based on actual treatment.

Major Analysis Protocol Deviations

Major analysis protocol deviations that could potentially affect the conclusions of the study will be identified prior to database lock. Major analysis protocol deviations include:

1. Study drug compliance defined as compliance < 80% or ≥ 120% over the interval from first to last dose for the treatment period,

Subjects with major analysis protocol deviations will be identified before the database lock.

6.4.5. Examination of Subgroups

The following subgroups are pre-defined:

1. Sex: [a] male, [b] female
2. Baseline hormone control: [a] severe/moderate control issues, [b] mild control issues
3. Baseline Glucocorticoid category: [a] Non-Dexamethasone [b] Dexamethasone

Selected analysis will be conducted using the subgroup analysis sets.

6.5. Baseline Definition

The following table indicates the baseline to be used in the analysis.

Table 2: Baseline Specifications for Specific Variables

Parameter	Day 1 pre-dose
Laboratory (Chemistry, Hematology, Urinalysis)	x
Biomarkers	x
ECG	x
Vital signs	x
PROs	x

6.6. Derived and Transformed Data

6.6.1. General Variable Definitions

Baseline Age

Subject's age in years will be calculated based on date of informed consent date using the following formula:

Age (year) = FLOOR ((date of informed consent – date of birth)/365.25*12) where FLOOR ( ) function returns the integer part of the result.

Study Day

If the date of interest occurs on or after the first dose date, then study day will be calculated as (date of interest – date of first dose) + 1.

If the date of interest occurs prior to the first dose date, then study day will be calculated as (date of interest – date of first dose).

There is no study day 0.

BMI

BMI will be calculated and converted to metric units by the following:

$$BMI\left(kg/m^2\right)=\frac{weight\left(kg\right)}{height\left(m\right)^2}.$$

6.6.2. Safety Variable Definitions

Compliance

% Compliance = percentage of study drug actually taken compared to what was expected based on the planned dose in time period *i* (where subject is receiving a constant dose), calculated as follows:

$$\%Compliance_i = 100 \times \left(\frac{\#\ Dispensed - \#\ Returned}{\#\ Dispensed - \#\ Expected\ Returned}\right)_i$$

Treatment Emergent Adverse Events

Adverse events (AEs) are recorded from signing of the informed consent form through the final follow-up assessment.

Adverse events observed prior to first dose are non-treatment emergent.

Treatment emergent adverse events are events with a start date/time after the first dose date/time until the last dose date/time plus the protocol defined follow-up period, 30 days.

Adverse events observed after the last dose and after the follow-up period are non-treatment emergent.

Only treatment-emergent AEs will be summarized in the tables.

6.6.3. Efficacy Variable Definitions

Baseline Hormone Control

Severe: Baseline ACTH > 4x ULN and A4 > 2x ULN

Moderate: Baseline ACTH > 2x ULN and A4 > 2x ULN

Severe/Moderate: Baseline ACTH > 2x ULN and A4 > 2x ULN

Mild: Baseline ACTH ≤ 2x ULN and A4 ≤ 2x ULN

Hormone Control Responder

Week 12 ACTH < ULN and A4 < ULN

Hydrocortisone equivalents

Hydrocortisone equivalent (mg) = Corticosteroid (mg) × Conversion Factor, using the following corticosteroid dosages equivalence table (reference is hydrocortisone 20 mg):

Medication	Equivalent Dose	Conversion Factor
Cortisone Acetate	25 mg	0.8
Hydrocortisone	20 mg	1
Prednisone/Prednisolone/ Methylprednisolone	4 mg	5
Dexamethasone	0.25 mg	80
Betamethasone	0.6 mg	33.33

For example, if a subject receives 10 mg of prednisone, that is equivalent to 50 mg of hydrocortisone.

Upper limit of Normal (ULN)

The following are the upper limit of normal or targets based on the lab reference ranges.

Hormone	SEX	ULN/Target
Serum 17-OHP	males	< 1200 ng/dL
Serum 17-OHP	females	< 1200 ng/dL
ACTH	males	< 63.3 pg/mL
ACTH	females	< 63.3 pg/mL
A4	males	< 152 ng/dL
A4	females	< 262 ng/dL

6.6.4. Visit Windows

All assessments will be summarized using analysis windows.

The terminology of unscheduled will be applied to assessments that are outside an analysis window regardless, of the nominal label associated with the assessments in the EDC system.

The following visit windows will be used in the summary of clinical data.

Table 3: Analysis Visit Windows

Nominal Period/Visit	Start (days)	Stop (days)
Baseline	1	1
Week 2 (Day 15)	2	21
Week 4 (Day 29)	22	35
Week 6 (Day 43)	36	49
Week 8 (Day 57)	50	63
Week 10 (Day 71)	64	77
Week 12 (Day 85)	78	91
Week 16 (Day 112)	92	120

Safety Endpoints

The following windows summarize the definition of treatment-emergent.

Table 4: Analysis Windows for Safety Endpoints

Window	Start	Stop
Adverse events	Sign of ICF	30 days post last dose
Treatment-emergent Adverse events, ECGs and Labs	Post first dose	Last dose + 30 days
Prior Medications	Prior to first dose	First dose
Concomitant Medications	Post first dose	Last dose + 24 hours
Post Medications	Post last dose + 24 hours	NA

6.6.5. Multiple Assessments

In general, if multiple, valid, non-missing observations exist at a visit or collection time point then records will be chosen based on the following rules.

The record closest to the nominal time point in question.

If 2 records are equidistant: later record if the two visits.

If 2 records with same date/time: average (generally applies to assessments done in triplicate).

6.7. Handling of Missing Data

6.7.1. Missing Efficacy Endpoints

Missing data will not be imputed for continuous efficacy endpoints in primary or secondary analyses.

A sensitivity analysis will impute missing hormone data using last observation carried forward.

For binary efficacy endpoints, missing data will be assumed as a failure (subject did not meet the efficacy endpoint).

6.7.2. Adverse Events Severity

For graded adverse event summaries, AEs with no grade reported will be graded as severe.

6.7.3. Missing Start and Stop Dates for Adverse Events

Missing start date and times will be handled as follows:

- AE onset date completely missing:
  - If AE is not ongoing and AE onset date missing and AE end date missing, then impute AE onset as date/time of first dose.
  - Else if AE is not ongoing and AE onset date missing and AE end date not missing and date/time of first dose <= AE end date, then impute AE onset as date/time of first dose of study drug.
  - Else if AE is not ongoing and AE onset date missing and AE end date not missing and AE end date is BEFORE first dose of study drug, then impute AE onset as AE end date YEAR and MONTH with 01 as the day and 00:00 as time.
  - Else if AE IS ongoing and AE onset date missing, then impute AE onset as date/time of first study drug dose.
- AE onset date has year and month only:
  - If AE onset date has year and month only and they are the year and month of first dose of study drug, then impute AE onset as date/time of first dose:
  - Else if AE onset date has year and month only and date/time of first dose is not missing, then impute AE onset as AE onset year and month with 01 as the date and 00:00 as the time.
- AE onset date has year only:
  - If AE onset date has year only and it is year of first dose of study drug, then impute AE onset as date/time of first dose of study drug.
  - Else if AE onset date has year only and date of first study drug dose is not missing and year of AE onset is NOT the year of first dose of study drug, then impute AE onset as Jan. 1 of the AE onset year and 00:00 as the time.
- AE onset missing (where it was not handled by the above cases):
  - If AE onset date is missing, then impute AE onset as date/time of first study drug dose.
- AE onset has complete date but missing time:
  - If AE onset date is a date only and is same as date of first study drug dose, then impute AE onset as date/time of first study drug dose.
  - Else if AE onset date is a date only and is NOT = date of first study drug dose, then impute AE onset as AE onset date with 00:00 as the time.

Missing end date and times will be handled as follows:

- AE end date - completely missing:
  - If AE if not ongoing and both AE onset and AE end dates are missing, then impute AE end date as date/time of last study drug dose.
  - Else if AE is not ongoing and AE onset date not missing and AE end date missing AND AE onset date <= date/time of last dose, then impute AE end date as date/time of last study drug dose.
  - Else if AE is not ongoing and AE onset date is not missing and AE end date is missing and date of last dose is not missing and AE onset is AFTER date of last dose, then impute AE end date as the last day of the month of AE onset date, with 23:59 as time.
- AE end date = year and month only:
  - If AE is NOT ongoing and AE end date consists of year and month only, then impute AE end date as the last day of the month of AE end date month and year, with 23:59 as time.
- AE end date = year only:
  - If AE is NOT ongoing and AE end date consists of a year only, and year = year of AE onset and AE onset date <= date of last study drug dose, then impute AE end date as the date of last study drug dose.
  - Else if AE is NOT ongoing and AE end date consists of a year only, and year = year of AE onset and AE onset date > date of last study drug dose, then impute AE end date as the year and month of AE onset, with the last day of the month as the day, and 23:59 as the time.
- AE end date = complete date but no time:
  - If AE is NOT ongoing and AE end date consists of a complete date but no time, then impute AE end date = trim (AE end date) || "T23:59".

6.7.4. Missing Start and Stop Dates for Medications

To determine whether medications were used prior to initiation of dosing and whether they were used after initiation of dosing, missing or partial dates for medications will be imputed according to the following rule:

Missing medication start date/time:

- If only have a YEAR, impute as Jan. 1, at one minute after midnight.
- Else if only have YEAR and MONTH, impute as Day 1 of month, at one minute after midnight.
- Else if have a complete date, impute TIME as one minute after midnight.
- Else if completely missing, and ((end date is present and >=date of first dose) or (end date is missing and is marked as "ONGOING")), impute as date and time of first dose. If missing and end date/time is present and prior to date of first dose then leave as missing.

Missing medication end date/time:

- If only have a YEAR and it is same as year of study completion, impute as date of study completion with time of 23:59.
- Else if only have a YEAR, impute as December 31 with time of 23:59.
- Else if only have YEAR and MONTH, then impute to last day of the month, with time of 23:59.
- Else if have a complete date but no time, impute time of 23:59
- Else if end date/time completely missing and not flagged as Ongoing, impute as date of study completion with time of 23:59.

Otherwise missing, no imputation.

6.7.5. Laboratory Data

For non-efficacy laboratory data, a missing baseline value will be replaced with the last available assessment, generally the screening assessment. A retest value will be used if the first test is invalidated, e.g., specimen hemolyzed.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation/limit of detection (LOD) will be, in general, imputed as follows:

- A value that is 1 unit less than the LOD will be used for calculation of descriptive statistics if the data are reported in the form of "< x" (x is considered as the LOD). More specifically, x−1 is used for data summarization if the data are reported in the form of "< x"; and x.e where e = d−1, will be used for analysis if the data are reported in the form of "< x.d";
- The LOD will be used for calculation of descriptive statistics if the data is reported in the form of "≤x" or "≥x.

7. STUDY POPULATION

7.1. Enrollment by Investigator

Enrollment by investigator will summarize the number of subjects enrolled by investigator by treatment group and total, sorted by highest enroller first.

The randomized analysis set is used to for this summary.

7.2. Subjects Disposition

Subject disposition information will be summarized for all subjects by dose. Summaries will include:

Label	Reporting Format
Subject Enrolled	F
Subjects Enrolled and Treated with Study Drug	F
Subjects Enrolled and NOT Treated with Study Drug	F
Subjects Completing Study	F
Subjects Not Completing Study	MF; Adverse event, Lost of follow-up, Non-compliance with study drug, Physician Decision, Pregnancy, Protocol Violation, Study terminated by Sponsor, Other

A listing of subject disposition will include the ITT analysis set status, the date of informed consent signed, the date of first dose and last dose of study drug, primary reason for subject discontinuation of study medication, the date of last visit, study completion status, primary reason for study termination, and the date of last contact.

The randomized analysis set is used to for this summary.

7.3. Protocol Deviations

A summary of protocol deviation identified prior to database lock by site will be provided.

In addition, 2 listings will be provided, a listing of protocol deviation identified prior to database lock and a listing of protocol deviation identified post database lock. The second listing will compose any new protocols derivations identified during site close out visits.

In addition, a listing of all major analysis protocol deviations will be provided.

The randomized analysis set is used to for this summary.

7.4. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized.

Label	Reporting Format
Subject Age	C
Sex	MF; Male, Female, Missing
Ethnicity	MF; Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown, Missing
Race	MF; White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Multiple Race, Missing
Baseline Weight (kg)	C
Baseline Height (cm)	C
BMI (kg/m^2)	C

A listing will also be provided.

7.5. Listing of Subject Inclusion and Exclusion Criteria

A listing of Inclusion and Exclusion criteria will be provided.

7.6. Medical History and Medical Conditions Present at Entry

Medical history will be summarized by treatment group, system Organ class and preferred term.

7.7. Prior Medication History and Medications Present at Entry

Prior Medications will be listed and summarized separately.

Summaries will be provided for glucocorticoid medications and prior medications summarizing medication name by the number and proportions of subjects with use.

Coding logic for each group is in Appendix Section 11.2.

7.8. Baseline Clinical Characteristics

A summary of Baseline Hormones will be provided:

Label	Reporting Format
Baseline Serum 17-OHP	GM
Baseline ACTH	GM
Baseline Androstedione (A4)	GM

7.9. Mini International Neuropsychiatric Interview

The number and percent of subjects answering affirmatively (i.e., "yes") to the questions in the Mini International Neuropsychiatric Interview (MINI) (version 7.0.2) questionnaire will be tabulated by individual cohort and overall.

The topics of the questionnaire include past and current instances of Major Depressive Episode, Suicidality, Manic/Hypomanic Episodes, Bipolar I and II Disorders, and Psychotic Disorders (including Major Depressive Episodes or Bipolar Episodes with Psychotic Features).

8. SAFETY AND TOLERABILITY

The analysis of safety and tolerability data includes an overall summary of tolerability, adverse event preferred terms by body/organ system, drug exposure (duration of treatment), dosing information/compliance, concomitant medications, clinical laboratory results, vital signs and ECGs. Tables summarizing the adverse events reported by subjects who died, experienced non-fatal serious adverse events (SAE), or prematurely discontinued the study due to adverse event (AEs) will be prepared. Summaries of potentially clinically notable laboratory results and vital sign abnormalities are presented.

In general, inferential statistical tests are not performed for adverse event incidence rates.

For all safety analyses, the safety analysis population will be used.

8.1. Adverse Event Preferred Term and Body/Organ System Summary Tables

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will present by system organ class (SOC), preferred term (PT) and severity and/or relatedness, the frequency and percentage of subjects reporting each observed event.

A treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus the number of days in the follow-up period. AEs observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from TEAEs.

All AEs and all TEAEs will be listed by subject.

Subjects who experienced treatment-limiting AEs will be listed. Treatment-limiting AEs are defined as any event that leads to permanent or temporary discontinuation from treatment, or a reduction in the treatment dose.

Summary of adverse events will be dependent on adverse events observed. If no adverse events meeting a specific table are observed, the summary table will not be completed. Blank summary tables will not be utilized.

The following is the list of adverse event tables:

Overall:

- Overall Summary of Adverse Events

Label	Reporting Format
Adverse Event	F
Moderate or Severe Adverse Event	F
Adverse Event Related to Study Drug	F
Moderate or Severe Adverse Event Related to Study Drug	F
Serious Adverse Event	F
Serious Adverse Event Related to Study Drug	F
Adverse Events Leading to Permanent Study Drug Discontinuation	F
Adverse Events Leading to Temporary Interruption of Study Drug	F
Death During Study	F

By preferred term:

- Treatment-emergent Adverse Events by PT
- Treatment-emergent Adverse Events by SOC and PT

By severity:

- Treatment-emergent Adverse Events by SOC, PT and Severity
- Serious Adverse Events
- Deaths during Study

By relatedness:

- Drug-Related Treatment-emergent Adverse Events by SOC and PT
- Drug-Related Treatment-emergent Adverse Events by SOC, PT and Severity
- Drug-related Serious Adverse Events

Other:

- Adverse events leading to premature study drug discontinuation

8.2. Total Duration of Therapy and Compliance

Study drug exposure (Number of doses) will be summarized using the 8-point descriptive summary. The source for exposure data is the drug accountability data domain.

Study drug compliance will be assessed using the following categories using the same source as the drug exposure data:

Label	Reporting Format
≥100%;	F
95%;	F
90%;	F
80%;	F

Study drug administration (date/time and study day) will be provided in a data listing. The source for study drug administration is the diary data domain.

8.3. Concomitant and Other Medications

Concomitant medications, prescribed and over the counter, that the subject takes or continues to take after the baseline visit will be summarized according to the following rules.

Medications with a start date before the date of the first dose of study medication will also appear in the prior medication summary table. The same summary format applies here as it was described for the medication history and medications present at study entry tables with respect to major drug class, minor drug class, and generic name. The data will be presented by treatment group and for all treated subjects. The same subject counting procedures will also apply (e.g.,

major class frequencies will represent subjects only once even though the same subject can be counted for multiple minor sub-classes and generic names).

The supportive individual subject data listing should be organized as the medication history listings with trade and generic drug names, start and stop dates, days relative to the start of therapy, dose, frequency, route, and indication(s).

8.4. Routine Laboratory Data

Laboratory data, hematology, serum chemistry and urinalysis, will be summarized in terms of observed values, changes from baseline for each period. In addition, changes from baseline for each period relative to normal ranges (e.g., shifts from normal to abnormal high/low) will be summarized in hematology: shift from baseline, serum chemistry: shift from baseline and urinalysis: shift from baseline.

Listings will flag laboratory values that are outside of normal range.

A listing of all abnormal lab values will be provided.

8.5. Vital Signs

For each nominal time point, vital signs will be summarized in terms of observed values and changes from Baseline. Outlier values of vital signs will be flagged in the listing.

Table 5: Vital Signs Outlier Thresholds

Heart Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
<40 >110	<85 >160	<45 >100

8.6. ECGs

A summary of ECG parameters, parameters reported separately QTcF, PR interval, QT interval, QRS duration, RR, and HR, will be summarized in terms of observed values and change from baseline.

Subjects without post-baseline measurement for a given treatment period will be excluded from the summary statistic (e.g., denominator of the summary statistic) for that time point.

All recorded values by central reader at ECG core lab for the standard 12-lead electrocardiogram parameters will be presented in a by-subject listing.

Outlier Analysis

The number of subjects with absolute ECG values and change from baseline in the ranges shown in Table 6 will be presented in Electrocardiogram Outlier Summary by Visit and Time Point.

In addition in the same summary, QTcF will also be summarized by the following categories, Normal (males <430, females ≤450), Borderline (males (>430, ≤450); females (>450, ≤470)) and Prolonged (males >450, females >470).

Individual ECG data collected during the study will be presented in a listing. A separate listing of subjects with values of QTcF > 500 msec or an increase > 60 msec will be provided, as necessary.

Figures

Cumulative distribution plots will be provided for maximum change in QTcF at Week 12.

Investigator Assessment of ECG Readings

The investigators' assessment of ECGs as normal, abnormal and clinically significant, or abnormal but not clinically significant will be summarized for baseline and for each visit.

Table 6: ECG Outlier Thresholds

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percentage Change from Baseline (%)	QRS Interval (msec)	QT_cF (msec)	QT_cF change from Baseline (msec)
>120	>20	> 200	> 15	> 120	Males:	≤ 30
>130	>30	> 220	> 25		≤ 430	>30, ≤ 60
					> 430	> 60
					> 450	
					> 470	
					> 480	
					> 500	
					Females:	
					≤ 450	
					> 450	
					> 470	
					> 480	
					> 500	

8.7. Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale is a 14-question scale. Seven questions compose the anxiety domain with scores of 0 to 3 with 3 representing a maximum response and 0 representing a minimal response. Seven questions compose the depression domain with scores of 0 to 3 with 3 representing a minimal response and 0 representing a maximal response.

The summary will summarize the anxiety, depression and total scores at each time point using a continuous reporting format.

8.8. 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. This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior, and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes "yes" or "no" responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

Tables will include results from the Suicidal Ideation and Suicidal Behavior sections of the C-SSRS. Frequencies and percent of subjects with a response of "Yes" at any point on the Suicidal Ideation and Suicidal Behavior items will be summarized by overall subjects. Screening (lifetime and past 6 months), baseline ("pre-treatment"), and post-baseline ("post-treatment") results will be presented.

Suicidality data collected on the C-SSRS will be listed for all subjects.

8.9. Testicular Ultrasound

A testicular ultrasound will be performed before first dose and at Week 12 in selected male subjects. If there are testicular adrenal rest tumors (TART) lesions present at baseline, a change in tumor size (i.e., sum of the size of all tumors) after treatment will be summarized by cohort and overall male subjects with TARTs at baseline in the FAS. Additionally, change in the number of TARTs from baseline to postbaseline will be summarized. In this context, baseline is the value before first dose.

If historical TART data exist, they will be presented in a listing along with the ultrasound

9. EFFICACY

9.1. General Considerations

For all efficacy data analyses, the safety analysis set will be used unless otherwise specified.

For all endpoints, nominal p-values will be provided.

9.2. Statement of the Null and Alternate Hypotheses for the Hormone Endpoints

The estimate of interest, change from baseline [17-OHP; ACTH; A4; Testosterone], is used to evaluate the effectiveness of SPR001 therapy in CAH subjects.

The following hypothesis testing schema will be employed to assess each endpoint:

The null hypothesis for the comparison will be that there is no difference between the baseline and the Week 12 mean response for [17-OHP; ACTH; A4; Testosterone].

The alternative hypothesis will be that there is a difference.

9.3. Subgroup Analyses

Subgroup analyses will characterize the consistency of the treatment effect across select subject subgroups. Subgroups analyses using the pre-specified subgroups in Section 6.4.5 will repeated for select analyses as specified in subsequent SAP sections.

9.4. Multiple Comparisons and Multiplicity

No control for multiplicity is planned given the hypothesis generating nature of this study.

9.5. Analysis of Secondary Efficacy Endpoints

Analysis of hormone data will be conducted only on subgroups.

9.5.1. Efficacy Analysis of Hormones

Hormones [17-OHP; ACTH; A4; Testosterone] will be summarized using geometric means and geometric means ratios to assess change and percentage change.

A summary of [17-OHP; ACTH; A4; Testosterone] by Visit will include the observed parameter (using GM reporting format).

Figures

A serial figure with week as the x-axis and % change as the y-axis will be provided.

Separate serial figures will be provided for each hormone.

9.5.2. Efficacy Analysis of Hormones by Subgroups

To characterize the consistency of the treatment effect for the primary endpoint, each hormone will be summarized using a combination of subgroups

A summary of [17-OHP; ACTH; A4; Testosterone] by Visit: [subgroup] will be provided. The following subgroups will be summarized in separate summaries:

- Non-Dexamethasone subjects
- Non-Dexamethasone subjects with severe/moderate control issues
- Non-Dexamethasone subjects with mild control issues

Figures

A serial figure with week as the x-axis and % change as the y-axis will be provided.

Separate serial figures will be provided for each hormone.

9.6. Analysis of the Exploratory Efficacy Endpoints

9.6.1. Patient Reported Outcomes

Data for the SF-36 (individual domain scores and summary scores), and total score for the CAH signs and symptoms interview will be summarized using descriptive statistics and presented by visit.

Data for PGIC will be summarized using counts and percentages for each SPR001 dose level.

9.6.2. Changes in Lipid Profile

The following parameters will be repeated from the standard lab output and as a standalone summary, changes in lipid profile summary by visit:

- Cholesterol
- HDL Cholesterol
- LDL Cholesterol
- Triglycerides

9.6.3. Changes in Insulin profile

The following parameters will be repeated from the standard lab output and as a standalone summary, changes in insulin profile summary by visit:

- Hemoglobin A1C
- Glucose

9.6.4. Changes in Body Weight

The following parameters will be repeated from the demog summary by visit as a standalone summary, changes in body weight profile summary by visit:

- Body weight
- BMI

9.6.5. Bother Score

Subjects scored their most bothersome symptom (symptom was not collected) on a scale of 1 (not bothersome) to 7 (most bothersome; bothersome all the time). A summary of the magnitude of bothersome symptoms will summarize the score and change from baseline in the score using the C reporting format.

10. REFERENCES

No references.

11. APPENDICES

11.1. Reporting Formats

C: Continuous endpoints will be presented with an 8-point summary using the following reporting structure, unless otherwise noted,

N	x
Mean (SD)	x.xx (x.xxx)
Median	x
Q1, Q3	xx.x, xx.x
Minimum, Maximum	xx.x, xx.x

GM: Continuous endpoints reported in log scale with a Geometric mean

n	x
Geometric Mean (CV)	x.xx (x.xxx)
95 CI for Geometric mean	x.xx, x.xx
95 CI for Geometric mean Ratio (GMR)	x.xx
95 CI for GMR	x.xx, x.xx
Percentage Change from Baseline	0.xx
95% CI for Percentage Change	x.xx, x.xx

F: Frequency endpoints will be presented by a 3-point summary using the following reporting structure, unless otherwise noted,

Count (%)	x (xx.x)

MF Categorical variables (multiple frequency) will be presented by a 3-point summary using the following reporting structure, unless otherwise noted, where the sum of the category n's is the total n

n	x
Category 1 count (%)	x (x.x)
Category 2 count (%)	x (x.x)

11.2. Medication Logic

Drug Class	Drug Name/ Classification
GLUCOCORTICOIDS	ATCtext4 = GLUCOCORTICOIDS

11.3. Tables, Figures and Listings

This index may be updated post finalization of the SAP.

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15.2.2.2	Summary of ACTH by Visit: Non-Dexamethasone Severe/moderate Control Issues	Safety	Serial
15.2.2.3	Summary of ACTH by Visit: Non-Dexamethasone Severe/moderate Control Issues- LOCF	Safety	Serial
15.2.2.4	Summary of ACTH by Visit: Non-Dexamethasone Mild Control Issues	Safety	Serial
15.2.3.1	Summary of Androstenedione by Visit: Dexamethasone Subjects	Safety	Serial
15.2.3.2	Summary of Androstenedione by Visit: Non-Dexamethasone Severe/moderate Control Issues	Safety	Serial
15.2.3.5	Summary of Androstenedione by Visit: Non-Dexamethasone Severe/moderate Control Issues- LOCF	Safety	Serial
15.2.3.6	Summary of Androstenedione by Visit: Non-Dexamethasone Mild Control Issues	Safety	Serial
15.2.4.1	Summary of Testosterone by Visit	Safety	Serial

Number	Title	Analysis Set	Type
15.2.4.2	Summary of Testosterone by Visit: Males	Safety	Serial
15.2.4.3	Summary of Testosterone by Visit: Females	Safety	Serial