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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Spruce Biosciences, Inc. protocol number SPR001-201, A Phase 2, Multiple-Dose, Dose-Escalation Study to Evaluate the Safety and Efficacy of SPR001 in Adults with Classic Congenital Adrenal Hyperplasia (CAH), dated 23-Aug-2018, version 3.1.

The statistical plan described hereafter is an *a priori* plan prior to database lock. Post-hoc exploratory analyses not identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The analysis of pharmacokinetic (PK) parameters is outside the scope of this document. Preliminary analysis between derived PK parameters and PD parameters is within the scope of this document.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objectives of the study are:

- To evaluate the safety of SPR001 in subjects with congenital adrenal hyperplasia (CAH); and
- To assess the efficacy of SPR001 in subjects with classic CAH as measured by percent and absolute change in serum 17-hydroxyprogresterone (17-OHP) compared to baseline.

2.1.2. Secondary Objectives

The secondary objectives of the study are:

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

2.1.3. Exploratory Objective

The exploratory objective of the study is:

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

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Adverse events (AEs), including identifying any dose limiting toxicities (DLTs),
- Change from baseline in safety laboratory, vital signs, and electrocardiogram (ECG) parameters,
- Clinical changes as determined by physical examinations (including testicular ultrasound for males),
- Depressive symptomatology as measured by the Beck Depression Inventory-II (BDI-II),
- Suicidality as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS), and
- Hospital Anxiety and Depression Scale (HADS)
- Concomitant medication usage.

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the change from baseline in serum 17-OHP AUC (10pm-8am; PM Period).

2.2.2.2. Secondary Efficacy Parameters

Secondary efficacy parameters of this study are:

- Change and percent change from baseline in plasma or serum biomarkers: ACTH, androstenedione (A4), and testosterone,
- Changes in CAH signs and symptoms total score,
- Changes in the Short Form 36 (SF-36), and,
- Changes in the Patient Global Impression of Change (PGIC).

2.2.2.3. Exploratory Endpoints

The exploratory efficacy endpoint of this study includes:

- PD biomarkers in saliva as measured by the change from baseline by dose,
- PD biomarkers in urine as measured by the change from baseline by dose.

2.2.3. Pharmacokinetic/Pharmacodynamic Endpoints

The pharmacokinetic (PK) analysis described in this analysis plan is intended to provide a preliminary evaluation of the systemic exposure of SPR001 in subjects with CAH and the relationship with PD biomarkers.

The PK endpoints of the study include:

- Maximum drug concentration (C_{max})
- Time of maximum drug concentration (T_{max})
- AUC for each set of serial plasma samples associated with a dose of SPR001.

The PD endpoints of the study include:

- Change and percent change from baseline in PD markers (serum 17-OHP, ACTH, A4, testosterone, cortisol) concentration or AUC

Relationship between SPR001 PK concentration and PD markers will be evaluated.

3. Overall Study Design and Plan

3.1. Overall Design

Cohort A

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 of the protocol. 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 3.7. 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 2 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.

The Schedule of Assessments for Cohorts B/C/D is provided in Section 3.7. 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.

3.2. Sample Size and Power

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.

3.3. Study Population

The study population consists of male and female subjects, aged 18 or older, with 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.

3.4. Treatments Administered

Subjects in Cohort A will be instructed to take study drug daily at 10pm (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.

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 10am and 10pm, 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 10am 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 10pm, the subject will take the 10pm dose of study drug at bedtime.

3.5. Method of Assigning Subjects to Treatment Groups

Subjects will be entered a treatment dose/cohort based upon their order of enrollment.

3.6. Blinding and Unblinding

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

3.7. Schedule of Events for Cohort A

A detailed schedule of events for Cohort A is provided in Table 1.1.

Table 1.1 Schedule of Assessments for Cohort A

	Screen Phase	First Dosing Period		Ascending-Dose Period			Follow-up/ ET
		Baseline	Dose 1				
Visit No.	1	2a	2b	3	4	5	6
Study Day	-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	X	X	X	X	X	X	X
Vital signs and body weight	X	X	X	X	X	X	X
Physical examination	X	X	X6	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	X	X		X	X	X	X
Serum 17-OHP (single collection)	X						
Hepatitis B & C and HIV screening	X						
Pregnancy test (WOCBP only)	X	X		X	X	X	X

	Screen Phase	First Dosing Period		Ascending-Dose Period			Follow-up/ ET
Visit No.	**1**	**2a**	**2b**	**3**	**4**	**5**	**6**
Study Day	**-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**
Genetic sample		X					
Dispense study drug			X	X	X		
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		X1	X	X	X	X	
Abbreviated PK/PD assessments (SPR001, 17-OHP, ACTH, cortisol), androstenedione, testosterone – 8a							X3
Androstenedione, testosterone – 6a, 8a		X	X	X	X	X	
Salivary 17-OHP – 8a		X	X	X	X	X	X3
Phone visit, safety check			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.

3.8. Schedule of Assessments for Cohorts B/C/D

Table 1.2 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]	

[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]**
Vital signs and body weight	X	X	X	X	X
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.

	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

[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).

[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.

	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]**
Dispense study drug		**X[19]**			
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.

[18] Salivary 17-OHP should be collected at around the same time during the morning of each visit (between approximately 8a to 10a).

[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.

4. Statistical Analysis and Reporting

All final, planned analyses identified in the protocol and in this SAP will be performed after the last subject has completed his/her outpatient follow-up visit, all relevant study data have been processed and integrated into the analysis database, and the database has been locked.

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.3 or higher).

Continuous variable summaries will include the number of subjects (n) with non-missing values, arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum.

At each time point or visit, observed value, change from baseline and percent change from baseline will be summarized.

For some parameters, coefficient of variation (CV%), Q1, Q3, and geometric mean will also be provided. In addition, ratio of post-baseline geometric mean to baseline and its 95% Confident Interval (CI), as well as percent change from baseline in geometric means and its 95% CI will be presented.

Categorical variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population by dose, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each visit.

The planned dose levels after 14 days of dosing are:

Table 2: Planned Dose Levels

Cohort	Visit	Planned Dose Level	Treatment Duration
A	Visit 3	SPR001 200 mg QD	14 days
	Visit 4	SPR001 600 mg QD	14 days
	Visit 5	SPR001 1000 mg QD	14 days
B	Visit 4	200 mg BID	14 days
C	Visit 4	100 mg BID	14 days

Cohort is defined as Cohort A, Cohort B, Cohort C, and total (Pooled Cohorts A, B, C).

Sex is defined as male, female, and overall (i.e., total).

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean, median, Q1 and Q3) will be reported to 1 degree of precision more than the observed data and measures of spread (standard deviation) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and nominal *P* values will be reported. Corresponding 95% CIs will be presented for statistical tests, unless otherwise specified.

4.2. Interim Analysis and Data Monitoring

Safety, PK and PD data will be reviewed periodically to determine the appropriate starting dose and stepwise dosing paradigm.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Full Analysis Set (FAS):** The FAS includes all subjects who received at least 1 dose of study drug. This is population is identical to the Safety Population. The FAS will be used to analyze all background and safety data.
- **Pharmacodynamic (PD) Population:** The PD Population includes all subjects in the FAS who received at least 80% of study drug administrations, had no major protocol violations and have at least 1 serum/plasma sample with a quantifiable concentration of 17-OHP. The PD Population will be used to summarize all PD data.
- **PK/PD Population:** The PK/PD Population includes all subjects with at least 1 PK parameter (e.g., AUC, C_{max}) and at least 1 PD parameter (e.g., AUC for 17-OHP and ACTH or 6a-8a average for androstenedione and testosterone). The PK/PD Population will be used to summarize all PK/PD analyses.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

Unless otherwise indicated, the last non-missing observation recorded before the first dose of SPR001 will be used as the baseline observation for all calculations of change from baseline. Exceptions are as follows:

- For derived PD parameters (e.g., Avg_{6a-8a} or AUC(**10pm-8am; PM period)**), the last parameter calculated before first dose will be considered as baseline, e,g, Day -1 for Cohorts A, B and C
- For time-matched PD analyses, baseline will be the time of assessment in the baseline period that corresponds with the time point after first dose of study drug (e.g., 8 am at Visit 3 will have a baseline of 8 am at Visit 2a).

The specific baseline used in an analysis will be described in the relevant section in this SAP.

6.1.2. Adjustments for Covariates

No adjustment for covariates in planned,

6.1.3. Multiple Comparisons

No adjustment will be performed for multiple comparisons.

6.1.4. Handling of Dropouts or Missing Data

In general, missing data will not be imputed, except as described below and in Section 6.1.9.

For calculation of AUCs, missing data within a visit will be handled as follows:

- If an intermediate time point is missing, the time point will be considered as missing but AUC will be calculated with linear interpolation.
- Missing last time point will be imputed with Last Observation Carried Forward (LOCF).
- If both the starting and ending time points are missing, then the AUC will be set to missing; no imputations will occur.

6.1.5. Analysis Visit Windows

For all analyses, visits will be analyzed as scheduled. For PK/PD assessments, if the visit has more than repeated measurements, the later repeated measurement will be used for analysis.

6.1.6. Order of Column Headers

Dose levels and cohorts will be reported in the following manner (with or without a total column):

SPR001 100 mg BID (n=xx)	SPR001 200 mg BID (n=xx)	SPR001 200 mg QD (n=xx)	SPR001 600 mg QD (n=xx)	SPR001 1000 mg QD (n=xx)	SPR001 Total (n=xx)

Or

SPR001 Cohort A (n=xx)	SPR001 Cohort B (n=xx)	SPR001 Cohort C (n=xx)	SPR001 Total (n=xx)

The same order will be used in figures with change from baseline.

6.1.7. Pooling of Sites

All sites will be pooled together for analysis.

6.1.8. Derived PD/Efficacy Variables

- **AUC (10pm-8am; PM Period)** = area under the PD concentration versus time profile over the 10-hour sampling period (10 pm to 8 am), calculated using the linear trapezoidal method and the scheduled time points (10pm, 2am, 3am, 4am, 6am, and 8am) calculated as follows for Cohort A/B/C:

$$AUC_{(10pm-8am;PM\ Period)} = \sum_{x=1}^{5} \frac{1}{2}(C_x + C_{x+1})(t_{x+1} - t_x)$$

where t = total time elapsed (in hours); $t_x = x^{th}$ time point at which PD samples are collected (using the nominal time points); and C_x = PD concentration at the x^{th} time point.

- **AUC (10am-10am; 24 hr Period)** = area under the PD concentration versus time profile over the 24-hour sampling period, will be calculated using the linear trapezoidal method and the scheduled time points, 10am, 12pm, 1pm, 2pm, 3pm, 4pm, 5pm, 6pm, 8pm, 10pm, 2am, 3am, 4am, 6 am, 8am, and 10am hours post dose, for the PD parameters of Cohort B/C.

- **AUC (10am-10pm; AM Period)** = area under the PD concentration versus time profile over the 24-hour sampling period, will be calculated using the linear trapezoidal method and the scheduled time points, 10am, 12pm, 1pm, 2pm, 3pm, 4pm, 5pm, 6pm, 8pm, 10pm, for the PD parameters of Cohort B/C.

- **Avg_{6a-8a}** = average PD concentration of the 6 am and 8 am time points within a study visit. If one of the results within a study visit is missing, Avg_{6a-8a} will be set to the non-missing result.

- **Hydrocortisone equivalent (mg)** = Corticosteroid (mg) × Conversion Factor, using the following corticosteroid dosages equivalence table[4] (reference is hydrocortisone 20 mg):

Medication	Equivalent Dose	Conversion Factor
Cortisone Acetate	25 mg	0.8
Hydrocortisone	20 mg	1
Prednisone	4 mg	5
Prednisolone	4 mg	5
Triamcinolone	4 mg	5
Methylprednisolone	4 mg	5
Dexamethasone	0.25 mg	80
Betamethasone	0.6 mg	$33.\overline{3}$

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

- **% 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:

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

and total % compliance over the entire treatment period is calculated as:

$$\%Compliance = 100 \times \left(\frac{\sum_{i=1}^{k} (\#Dispensed - \#Returned)_i}{\sum_{i=1}^{k} (\#Dispensed - \#Expected\ Returned)_i} \right)$$

where

Σ represents the summation operator and the value in parentheses is summed over the sequence *i* = 1 to *k*, where

k = number of time periods subject is receiving a constant dose, and

possible constant dose levels are 200 mg through 1000 mg, in multiples of 200 mg.

- **Total SPR001 Dosage (mg)** = dosage of SPR001 taken over a specific study period *i* (where subject is intended to receive a constant dose, even if subject experiences a dose reduction), calculated as follows:

$$Total\ SPR001\ Dose_i = \left((\#Dispensed - \#Returned) \times Tablet\ Strength(mg) \right)_i$$

and total SPR001 dose over the entire study period is calculated as:

$$Total\ SPR001\ Dose = \sum_{i=1}^{k} (Total\ SPR001\ Dose)_i$$

where

Σ represents the summation operator and the value in parentheses is summed over the sequence *i* = 1 to *k*, where

k = number of time periods subject is intended to receive a constant dose, and

Tablet strength (mg) is 200 mg.

- **Mean Daily SPR001 Dose (mg/day)** = Total SPR001 Dose (mg) / Treatment Duration (days) for each planned dose level and over the entire study.
- **Treatment Duration (days)** = LASTDAY – FIRSTDAY+ 1 day,

where

LASTDAY is the date of last dose during the constant dosing period, and

FIRSTDAY is the date of first dose during the constant dosing period.

- **Absolute change from baseline** = value at time point of interest – value at baseline,

- **Percent change from baseline** = (absolute change from baseline / value at baseline) × 100%. If the value at baseline is 0 and the change from baseline is not 0, then percent change from baseline will be set to missing. However, if both the baseline and change from baseline values are both 0, then the percent change will be set as 0.

- **TEAE** = any AE with an onset date/time after first dose of study drug. If the time is missing and the date is on or after date of first dose of study drug, the AE will be considered as a TEAE.

6.1.9. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All p-values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0. XXXX). If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

For non-PK values that are presented as either above or below the respective quantitation limits, the following imputations will be made for the purposes of summarization:

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

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Concomitant medications will be coded using World Health Organization Drug Dictionary B2-Enhanced (WHO-DD B2E) (March 2017).

A treatment related AE is any AE with a relationship to the study drug of possibly related, probably related, or definitely related.

If partial start dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows:

- If just day is missing, then do the following:
    - If it is an AE partial start date and the AE is marked as being before the first dose on the CRF, the day assigned is the first day of the month;
    - If it is an AE partial start date and the AE is not marked as being before the first dose on the CRF, or if the partial start date is another data type, the day assigned is the day of the date of first dose.
- If just month is missing, then do the following:
    - If it is an AE partial start date and the AE is marked as being before the first dose on the CRF, the month assigned is the month of the first dose, unless that results in a date after the first dose, in which case the month before the first dose is used; or

    - If it is an AE partial start date and the AE is not marked as being before the first dose on the CRF, or if the partial start date is another data type, the month assigned is the month of the first dose, unless that results in a date before the first dose, in which case the month after the first dose is used.
- If both month and day are missing, then do the following:
    - If it is an AE partial start date and the AE is marked as being before the first dose on the CRF, set as the first day of the month of first dose date, unless first dose date occurred on that month; in that case, assign as the last day of the previous month; or
    - If it is an AE partial start date and the AE is not marked as being before the first dose on the CRF, or if the partial start date is another data type, the month and day assigned is the first dose date.
- If the year is unknown, then do not impute the date but assign a missing value.

If the imputed start date is after the known end date, then do the following:

- If it is an AE partial start date and the AE is marked as being before the first dose on the CRF, and the AE end date is after the first dose of study drug, set as the day before first dose of study drug;
- Otherwise, if the end date is after first dose date (or end date is missing), the start date will be set to the date after first dose.
- Otherwise, the start date will be set to the end date.

If partial end dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows:

- If just day is missing, then do the following:
    - If the month and year match the month and year of the last date of the study, the day assigned is the day of last date of the study (date of last contact if subject lost to follow-up; date of completion or early termination otherwise);
    - Otherwise, assign as the last day of the month.
- If just month is missing, then do the following:
    - If the year matches the year of the last date of the study, the month assigned is the month of the last date of the study; or
    - Otherwise, assign 31 December.
- If both month and day are missing, then do the following:
    - If the year matches the year of the last date of the study, the month and day assigned is the month and day of the last date of the study; or
    - Otherwise, assign 31 December.
- If the year is unknown, then do not impute the date but assign a missing value.

If the imputed end date is before the known or imputed start date, then the end date will be set to the last date of the study.

If partial times occur, the convention is as follows:

- if the missing time occurs on the day of the first dose and both the hour and minute are missing then do the following:
    - If it is an AE partial start date and the AE is marked as being before the first dose on the CRF, the time assigned is 12:00;
    - Otherwise, the time assigned is the time of the first dose.
- Otherwise if both the hour and minute are missing then do the following:
    - If the date is not the date of first dose the time assigned is 12:00;
    - If the date is the same as the date of the first dose and only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later; and
    - If the date is the same as the date of first dose and only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later;
    - Otherwise the hour assigned is 12 if the hour is missing and the date is not the same as the date of first dose and the minute assigned is 30 is the the date is not the same as the date of first dose.

These conventions will be applied only to AE, diagnosis of CAH, and prior and concomitant medication onset dates and times with the following precaution: if the missing date and time reflect the date and time of onset of an event/history/medication, the modified date and time will be constructed to match the first documented date/time post drug administration while preserving the order in which the event/history/medication was reported in the case report form (CRF).

7. Changes from Planned Analysis

The protocol indicates that the primary parameter for analysis for an exploratory assessment of drug-drug interactions with exogenously administered glucocorticoids will be AUC of cortisol for an exploratory assessment of drug-drug interactions with exogenously administered glucocorticoids; however, the measurement of cortisol is only applicable for subjects taking hydrocortisone.

Instead, the primary endpoint will be the change from baseline in the serum 17-OHP AUC (10pm-8am; PM Period), and it will be summarized for subjects without concomitant dexamethasone.

The protocol also indicates that a linear mixed model will be used to analyze PD measurements; based on the sample size of this study, that type of analysis will not be performed.

The protocol indicates an assessment of dose proportionality of SPR001 observed in this study will be investigated with the power model approach. This analysis will not be performed.

The protocol specifies the Per Protocol Population, but the per protocol analysis will not be performed

8. Study Subjects and Demographics

8.1. Enrollment by Investigator

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

The FAS analysis set is used to for this summary.

8.2. Disposition of Subjects and Withdrawals

Disposition will include summaries of the number of subjects enrolled in the study, the number of subjects dosed with study drug, the number of subjects who received each dose level, reasons for discontinuation from the study, the last dose level received for subjects who discontinued, and number of subjects in each analysis population. Tabulations will be presented by Cohort and overall.

8.3. Inclusion/Exclusion Criteria and Protocol Deviations

Inclusion and exclusion criteria not met will be listed.

Additionally, protocol deviations will be listed.

8.4. Demographics and Baseline Characteristics

The following demographic characteristics will be summarized for each cohort and in total on the same summary: age, sex, child-bearing potential (female subjects only), race, ethnicity, height, weight, body mass index (BMI), CAH disease duration, baseline glucocorticoid dose in Hydrocortisone equivalent (mg) and Screening 17-OHP concentration.

8.5. Medical History

Medical history will be summarized by Cohort, System Organ Class and Preferred Term. This will include historical instances of TARTs (for males).

8.6. Prior and Concomitant Medications

Prior and concomitant medications, coded using WHO-DD B2E (March 2017), will be summarized descriptively by Anatomical Therapeutic Chemical (ATC) classification Level 4 and preferred term by individual cohort and in total in the same summary.

Prior medications will be presented separately from concomitant medications. Medications that started prior to first dose of study drug will be considered prior medications whether or not they were stopped prior to first dose of study drug. Any medications starting after first dose of study drug will be considered to be concomitant. If a medication starts before first dose of study drug and continues after first dose of study drug, it will be considered both prior and concomitant; these medications will be counted at the SPR001 200 mg level for summaries.

Corticosteroid therapy regimens that subjects were on before entering the study will be summarized similarly to prior and concomitant medications, except it will be summarized by ATC classification Level 4 for preferred term and Level 3 for class (mineralocorticoid or glucocorticoid).

Number and percentage of subjects taking any steroid therapy during the study will be summarized by overall subjects within each cohort and overall. A table containing a by-subject listing with subject, steroid therapy(ies) received, total daily dose (based on actual therapy(ies)

received), and total daily dose based on hydrocortisone equivalents, as well as a summarization of the total daily dose based on hydrocortisone equivalents, will be presented by overall subjects within cohort.

8.7. 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).

These analyses will be conducted on the FAS.

9. Efficacy Analysis

All *P* values will be tested at the 2-sided $\alpha = 0.05$ significance level.

All efficacy data will be included in data listings.

9.1. Primary Efficacy Analysis

9.1.1. Primary Analysis of the Primary Efficacy Variable

The primary efficacy endpoint is the change from baseline in serum 17-OHP as determined by AUC (10pm-8am; PM Period) for all Cohorts.

The summary of the primary endpoint will include observed value (6-point summary), absolute change from baseline (6-point summary), percentage change from baseline (6-point summary), and geometric means.

The geometric mean ratio (GMR), Week2/Baseline, and associated 95% confidence intervals will be summarized. In addition, the GMR will be translated into a percentage change with associated 95% confidence interval.

P-values will be derived using paired t-tests.

The analysis population for these analyses will be the PD Population. The summary will be presented in the following order, a.) All (Females/Males), b.) Females and c.) Males d). Subjects without concomitant dexamethasone (DEX), with each summary on a separate page.

P-values will only be presented for the analysis (a).

9.2. Secondary Efficacy Analysis

9.2.1. Summary of Secondary Biomarker Parameters

Using the same reporting format as the primary analysis, the following parameters will be summarized:

- Serum 17-OHP at 8 am

- Serum 17-OHP Average 6-8 am
- Serum 17-OHP AUC (10am-10am; 24 hour)
- Serum 17-OHP AUC (10am-10pm; AM Period) [only cohorts B/C]
- ACTH at 8 am
- ACTH Average 6-8 am
- ACTH AUC (10pm-8am; PM Period)
- ACTH AUC (10am-10am; 24 hour) [only cohorts B/C]
- ACTH AUC (10am-10pm; AM Period) [only cohorts B/C]
- Androstenedione (A4) at 8am
- A4 Average 6-8 am
- A4 AUC (10pm-8am; PM Period) [only cohorts B/C]
- A4 AUC (10am-10am; 24 hour) [only cohorts B/C]
- A4 AUC (10am-10pm; AM Period) [only cohorts B/C]
- Testosterone at 8am
- Testosterone at Average 6-8 am
- Testosterone AUC (10pm-8am; PM Period) [only cohorts B/C]
- Testosterone AUC (10am-10am; 24 hour) [only cohorts B/C]
- Testosterone AUC (10am-10pm; AM Period) [only cohorts B/C]

9.2.2. Summary of Secondary Biomarkers by Time Point

Secondary biomarkers over time will be summarized using the same reporting format as the primary analysis where (Week 2) is replaced by individual time point. Reporting will be in the following order, a.) All, b.) Female, c.) Male and d.) Subjects without concomitant DEX, with all timepoints summarized within a group prior to proceeding to summarizing the next group.

Time point will be labelled by the nominal time (not time post dose). The baseline summary section will be repeated on each page with one page per time point.
The summary will be presented for two baseline analyses:

- Baseline is the Day baseline
- Time-matched baselines

These summaries will be provided for the following biomarkers:

- Serum 17-OHP
- ACTH
- A4
- testosterone

The analysis population for these analyses will be the PD Population.

9.3. Responder Analyses

9.3.1. Normalization of Biomarkers

A normalization responder is defined as meeting the responder criteria for a biomarker at either the 6 am or 8 am nominal time points. In addition, a best response over all dose levels will be

summarized for subjects in Cohort A (if subject has an observed positive response in either 200 mg QD, 600 QD or 1000 mg QD with dosing over 14 days).

Responder criterion:

- 17-OHP: observed value ≤ 1200 ng/dL
- ACTH: observed value ≤ 63.3 pg/mL
- A4: observed value ≤ 262 ng/dL for Females and ≤ 152 ng/dL for Males

The following biomarker groups will be summarized:

- 17-OHP
- ACTH
- A4
- 17-OHP and ACTH
- 17-OHP and A4
- ACTH and A4
- 17-OHP, ACTH and A4

Subjects in Cohort A will be summarized only once in the total column.

9.3.2. Observed Values as a Multiple of the Upper Limit of Normal

Subjects will be summarized (cumulatively) by multiples of the upper limit of normal (ULN) for each respective serum biomarker, 17-OHP, ACTH, and A4, at Baseline and after 14 days of dosing (week 2) using the following multiples:

- < 1x ULN
- < 2x ULN
- < 4x ULN
- ≥ 4x ULN

Subjects in Cohort A will be summarized only once in the total column.

In addition, a shift table will summarize the change in ULN category from Baseline to Week 2 using the following categories:

- < 1x ULN
- 1-2x ULN
- 2-4x ULN
- 4-10x ULN
- >10x ULN
- Missing

9.3.3. Biomarkers by Percent Change

Using the same reporting format as in section 9.3.1, a second responder definition is defined as subjects with ≥ 50% reduction from baseline. The same best response definition will be used for Cohort A subjects as in section 9.3.1.

The following biomarker groups will be summarized:

- 17-OHP
- ACTH
- A4
- 17-OHP and ACTH
- 17-OHP and ACTH
- ACTH and A4
- 17-OHP, ACTH and A4

Subjects in Cohort A will be summarized only once in the total column.

9.4. Patient-Reported Outcomes Analysis

Patient-Reported Outcomes were collected for cohort B and C subjects. Data for the SF-36 (individual domain scores and summary scores), HADS (anxiety subscale score, depression subscale score, and total score), 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.

Due to operational issues with wrong PRO versions, SF-36 will not be presented for Cohort B.

10. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs; changes in clinical laboratory values, vital signs, and electrocardiograms (ECG); physical examinations; testicular ultrasound; and depression and suicidal risk monitoring.

Safety data will be summarized descriptively. All safety analyses will be performed on the FAS. For all safety listings and tabular summaries, subjects will be summarized overall and by dose level within each cohort.

Individual subject listings will be prepared for all safety data.

10.1. Exposure and Compliance

Study drug compliance will be calculated for each subject and summarized descriptively for each dose level and overall for all dose levels, and by individual cohort. This analysis will be completed using the FAS.

Total drug exposure (mg), mean daily dose (mg/day), and total days of exposure will be summarized descriptively.

Study drug compliance and exposure listings will be prepared for all subjects.

Additionally, dose escalation and reduction information will be listed. Study medication and snack diary data will be listed.

10.2. 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 approximately 30 days after the final dose of study drug (ending with the 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.

The causal relationship of the AE to the study drug is determined by the investigator as Unrelated, Unlikely Related, Possibly Related, Probably Related, and Definitely Related. These can be mapped to Unrelated (Unrelated and Unlikely Related) and Related (Possibly Related, Probably Related, and Definitely Related).

Adverse event severity grades are reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3.

An AE summary table will be presented for the following:

- All TEAEs
- TEAEs by maximum severity
- TEAEs by strongest mapped relationship to study drug
- TEAEs leading to discontinuation of study drug
- Serious AEs (SAEs)
- DLTs
- TEAEs of special interest
- Deaths

Summaries of incidence rates (frequencies and percentages) of individual TEAEs by MedDRA (v20.0) system organ class (SOC) and preferred term (PT). Such summaries will be displayed for all TEAEs, TEAEs by maximum severity, and TEAEs by strongest mapped relationship (i.e., Unrelated or Related) to study drug. Analysis of TEAEs will be performed by overall subjects and dose level within cohort. Events will only be counted in the planned dose level in which the event started. For example, if an event starts at the 200 mg dose level and continues into 600 mg dose level, the event will not be counted at the 600 mg dose level. If an event starts or worsens in the follow-up period, that event will be summarized under the last treatment received.

Each subject will be counted only once within each summation level (SOC and preferred term). If a subject experience more than one TEAE within each summation level only, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity.

Incidences will be presented by descending frequency of SOC and PT within SOC, and then alphabetically within PT where the incidence is the same; this is based on overall subjects. Additionally, a table with incidences presented by descending frequency of PT (based on overall subjects) and then alphabetically by PT will be provided.

Missing and partially missing AE start and/or stop dates will be imputed, for the purpose of statistical analysis, according to the specifications described in Section 6.1.9.

A subject listing of all TEAEs will be presented. Disease-related events, as described in the protocol, will be flagged.

10.2.1. Adverse Events Leading to Discontinuation

A summary of incidence rates (frequencies and percentages) of TEAEs leading to discontinuation of study drug, by dose level, SOC, and PT will be prepared for subjects in the FAS. No inferential statistical tests will be performed.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF. Additionally, a data listing of AEs that trigger a stopping rule will be listed.

10.2.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious AEs will be listed and also tabulated by SOC and PT and presented by overall subjects and planned dose level.

10.2.3. Other Significant Adverse Events

A DLT is defined as a treatment-related Grade 3 (severe or medically significant but not immediately life threatening) or higher AE according to the CTCAE version 4.03. If a Grade 3 or worse event is clearly a non-treatment related event and therefore not a suspected adverse reaction, 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. A summary of incidence rates (frequencies and percentages) of DLTs (for dose escalation purposes) will be presented overall and by dose level, SOC, and PT on the FAS. All DLTs will be flagged in the listings.

The following AEs are of special interest in this study, and will be reported on an SAE form:

- 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 (e.g. hospitalization).
- High BDI-II scores (i.e., BDI-II≥29) or other indications of worsening depression and/or "changes in behavior."
- Liver function test (LFT) elevations deemed clinically significant that do not satisfy stopping rules per the protocol and cases of Hy's Law (reported as SAEs).
- Dose limiting toxicities (DLTs).

A summary of incidence rates (frequencies and percentages) of AEs of special interest (excluding DLTs, as they will be presented separately) will be presented by overall subjects and dose level, SOC, and PT on the FAS and flagged in the listings.

10.3. Clinical Laboratory Evaluations

Clinical laboratory assessments will be collected when the subjects first arrive at the clinic at all visits except for Visit 2b. All summaries of laboratory values will be presented using SI units. All hematology, chemistry (including liver function tests), urinalysis, reproductive hormones,

and other results will be listed by subject and timing of collection. Abnormal results will be flagged in the listings.

Observed values and change from baseline at each time point for continuous hematology, chemistry, urinalysis, and reproductive hormones results will be summarized using descriptive statistics by overall subjects within cohort. Categorical urinalysis results will be summarized using frequencies by overall subjects within cohort. Furthermore, reproductive hormone results will be summarized by sex. Shifts tables of change from baseline to each time point categorizing values as normal, low, and high will be performed for hematology, chemistry, reproductive hormones, and urinalysis results, as applicable.

Abnormal liver function tests (specifically, ALT, Bilirubin, INR) and Hy's Law (ALT ≥ 3 x upper limit of normal [ULN] and [Bilirubin ≥ 2 x ULN (>35% direct) or INR > 1.5, if measured)] will be presented in a data listing.

Pregnancy test results and hormonal laboratory results will be listed.

10.4. Vital Signs

Vital signs will be collected at each visit. Observed values and change from baseline will be calculated for weight, BMI, temperature, heart rate, systolic blood pressure, and diastolic blood pressure by overall subjects within cohort. All vital signs results will be listed.

10.5. Electrocardiograms

The 12-lead ECG will be conducted at each visit, except for Visit 2b. The following 12-ECG parameters will be listed for each subject: heart rate, PR interval, RR interval, QRS duration, QT interval, and QTcF interval, along with investigator interpretation. Observed values and change from baseline at each study visit will be summarized by overall subjects within cohort. Subjects with a QTcF value meeting stopping rules (observed QTcF > 500 msec or QT > 600 msec; change from baseline QTcF > 60 msec) will be flagged in the data listings.

10.6. Physical Examinations

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. All physical examination results will be listed.

10.7. Testicular Ultrasound

A testicular ultrasound will be performed before first dose and at Visit 5 (Days 41 to 42) 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 exists, this will be presented in a listing along with the ultrasound

findings.

10.8. Depression Monitoring

Depressive symptomatology will be monitored at all visits except for Visit 2b with the BDI-II, 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. Each answer is scored on a scale from 0 to 3, with higher total scores indicating more severe depressive symptoms. Responses on individual questions are summed up to form the total score. If an individual question is missing a response, the missing response will be imputed as a 3 (i.e., worst-case scenario). 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 total score will be summarized using descriptive statistics as well as categorized as follows:

- 0-13 = No/minimal depression
- 14-19 = Mild depression
- 20-28 = Moderate depression
- ≥29 = Severe depression

The BDI-II total score and categories at each planned dose level will be summarized by overall subjects within individual cohorts and overall (Cohorts A+B+C). A shift table of values at each visit relative to baseline assessment will also be presented

10.9. 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. 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).

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

11. Other Planned Analysis

11.1. Pharmacokinetic/Pharmacodynamic Analysis

Pharmacokinetic/pharmacodynamic relationships will be explored using derived PK parameters, SPR001 AUC, C_{max} and derived PD parameters, AUC by matched time point, 8 am assessment

and AVG(6/8). Relationships will be explored using figures.

Correlations between mean SPR001 plasma concentrations and mean change from predose as baseline in serum 17-OHP and ACTH, and mean change from time-matched baseline in androstenedione and testosterone will be plotted at common and matched study visits/time points. A trend line, Pearson correlation coefficient, and accompanying *P* value will be presented. All data points will be presented on 1 graph. This will be repeated on observed SPR001 plasma concentrations and observed serum 17-OHP, ACTH, androstenedione, and testosterone at comment and matched study visits and time points (separately for each analyte).

Similarly, plots of mean change from baseline in AUC of 17-OHP (Cohort A/B/C), ACTH (Cohort A/B/C) and androstenedione (Cohort B/C) versus AUC of SPR001 by matched time point will be presented, along with the overall correlation. All data points will be presented on 1 graph. $Avg_{6a\text{-}8a}$ of SPR001 will be compared to $Avg_{6a\text{-}8a}$ of serum 17-OHP, ACTH, androstenedione, and testosterone in the same way for Cohort A.

11.2. Exploratory Analysis

11.3. Salivary PD Marker Analysis

Salivary 17-OHP samples will be compared to serum 17-OHP samples to determine the degree of agreement/correlation between the two types of measurements. These results will be summarized by study visit at the matching time point. Summary statistics by visit will also be presented for the other salivary PD markers.

11.4. Exploratory Drug-Drug Interaction Analyses

In order to explore the effect of exposure to study drug on corticosteroid analyte levels, a figure plotting ratio of geometric means (on-treatment AUC vs baseline AUC) for all dose levels will be provided by cohort.

Additionally, absolute and percent change from baseline in corticosteroid analyte levels will be summarized for each study visit/dose level by overall subjects and sex within cohort. This summarization will be presented using 2 baselines as per Section 9.2: time-matched baseline and predose within a visit as baseline. A plot of arithmetic means and SD of absolute and percent change from baseline of corticosteroid analyte levels over time will be presented. This will include both time-matched baseline and predose within a visit baseline (2 presentations), as well as subject-level presentations. These analyses will only be performed on subjects taking a corticosteroid during the study.

12. References

1. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm
2. RSS. (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.
3. US Federal Register. (1998) International Conference on Harmonization; Guidance on

Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
4. Steven K. H. (1997) Adrenal cortical steroids. In: Drug facts and comparisons. 5th ed. St. Louis: Facts and Comparisons, Inc.; 122–128.

13. Tables, Listings, and Figures

All listings, tables, and figures (TLFs) will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path.

13.1. Planned Table and Figure Descriptions

The following are planned summary tables and figures for protocol number SPR001-201. The table and figure numbers and page numbers are place holders only and will be determined when the outputs are produced.

In addition, the list of TFLs may be expanded.

13.2. Demographic Data Tables

Table Number	Analysis Set	Table Title/Summary	Type
14.1.1.1	All Subjects	Enrolment by Investigator	Unique
14.1.1.2	All Subjects	Study Populations and Dose Levels	Unique
14.1.1.3	FAS	Subject Disposition	Unique
14.1.2.1	FAS	Demographics and Baseline Characteristics	Unique
14.1.2.2	PD	Demographics and Baseline Characteristics	Repeat (14.1.2.1)
14.1.3.1	FAS	Medical History	Unique
14.1.3.2	FAS	Mini International Neuropsychiatric Interview (MINI)	Unique
14.1.3.3.1	FAS	Prior Medications	Unique
14.1.3.3.2	FAS	Prior Corticosteroid Therapies	Unique

13.3. Efficacy Data Tables

Table Number	Analysis Set	Table Title/Summary	Type
14.2.1.1	PD	Summary of Serum 17-OHP AUC (10 pm-8 am; PM period)	unique
14.2.1.2	PD	Summary of Serum 17-OHP at 8 am	repeat (14.2.1.1)
14.2.1.3	PD	Summary of Serum 17-OHP Average (6-8 am)	repeat (14.2.1.1)
14.2.1.4	PD	Summary of Serum 17-OHP AUC (10am – 10am; 24 hour)	repeat (14.2.1.1)
14.2.1.5	PD	Summary of Serum 17-OHP AUC (10am – 10pm; AM period)	repeat (14.2.1.1)
14.2.2.1	PD	Summary of ACTH AUC (10 pm-8 am; PM period)	repeat (14.2.1.1)
14.2.2.2	PD	Summary of ACTH at 8 am	repeat (14.2.1.1)
14.2.2.3	PD	Summary of ACTH Average (6-8 am)	repeat (14.2.1.1)
14.2.2.4	PD	Summary of ACTH AUC (10am – 10am; 24 hour)	repeat (14.2.1.1)
14.2.2.5	PD	Summary of ACTH AUC (10am – 10pm; AM period)	repeat (14.2.1.1)
14.2.3.1	PD	Summary of Androstenedione (A4) at 8 am	repeat (14.2.1.1)
14.2.3.2	PD	Summary of Androstenedione (A4) (6-8 am)	repeat (14.2.1.1)
14.2.3.3	PD	Summary of Androstenedione (A4) AUC (10am – 10am; 24 hour)	repeat (14.2.1.1)
14.2.3.4	PD	Summary of Androstenedione (A4) AUC (10am – 10pm; AM period)	repeat (14.2.1.1)
14.2.1.1	PD	Summary of Testosterone at 8 am	repeat (14.2.1.1)

Table Number	Analysis Set	Table Title/Summary	Type
14.2.1.2	PD	Summary of Testosterone (6-8 am)	repeat (14.2.1.1)
14.2.1.3	PD	Summary of Testosterone AUC (10am – 10am; 24 hour)	repeat (14.2.1.1)
14.2.1.4	PD	Summary of Testosterone AUC (10am – 10pm; AM period)	repeat (14.2.1.1)
14.2.5.1	PD	Summary of Serum 17-OHP Concentrations (ng/dL) Time Point	Unique
14.2.5.2	PD	Summary of Time-Matched Serum 17-OHP Concentrations (ng/dL) by Time Point	repeat (14.2.5.1)
14.2.6.1	PD	Summary of ACTH Concentrations (pg/dL) Time Point	repeat (14.2.5.1)
14.2.6.2	PD	Summary of Time-Matched ACTH Concentrations (pg/dL) by Time Point	repeat (14.2.5.1)
14.2.7.1	PD	Summary of Androstenedione (A4) Concentrations (ng/dL) Time Point	repeat (14.2.5.1)
14.2.7.2	PD	Summary of Time-Matched Androstenedione (A4) Concentrations (ng/dL) by Time Point	repeat (14.2.5.1)
14.2.7.1	PD	Summary of Testosterone Concentrations (ng/dL) Time Point	repeat (14.2.5.1)
14.2.7.2	PD	Summary of Time-Matched Testosterone Concentrations (ng/dL) by Time Point	repeat (14.2.5.1)
14.2.8.1.1	PD	Summary of Normalization of Pharmacodynamic Biomarkers	Unique
14.2.8.1.2	PD-non-DEX	Summary of Normalization of Pharmacodynamic Biomarkers	Repeat (14.2.8.1.1)
14.2.8.2	PD	Summary of Week 2 Observed value by Upper Limit of Normal (ULN) Multiple	Unique
14.2.8.3.1	PD	Pharmacodynamic Biomarker Shift: Upper Limit of Normal Multiple at Week 2	Unique
14.2.8.3.2	PD-non-DEX	Pharmacodynamic Biomarker Shift: Upper Limit of Normal Multiple at Week 2	Repeat (14.2.8.3.1)
14.2.9.1.1	PD	Summary of Subjects with at least 50% Change from Baseline	Repeat (14.2.8.1)
14.2.9.1.2	PD-non-DEX	Summary of Subjects with at least 50% Change from Baseline	Repeat (14.2.8.1)
14.2.10.1	PD	Summary of Salivary Pharmacodynamic Biomarkers by Visit and Cohort	Unique
14.2.11.1	PD	Correlations between Salivary 17-OHP (ng/dL) and Serum 17-OHP (ng/dL) by Dose Level	Unique
14.2.12.1	FAS	Summary of SF-36 (Acute Form) by Visit	Unique
14.2.13.1	FAS	Summary of PGIC by Visit	Unique
14.2.14.1	FAS	Summary of CAH Signs and Symptoms Questionnaire Total Scores	Unique

13.4. Safety Data Tables

Table Number	Analysis Set	Table Title/Summary	Type
14.3.1.1	FAS	Study Drug Exposure	Unique
14.3.2.1	FAS	Study Medication Compliance	Unique

Table Number	Analysis Set	Table Title/Summary	Type
14.3.3.1.1	FAS	Treatment-Emergent Adverse Events Overall Summary	Unique
14.3.3.1.2	FAS	Treatment-Emergent Adverse Events by Preferred Term	Unique
14.3.3.1.3	FAS	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Unique
14.3.3.1.4	FAS	Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term	Repeat (14.3.3.1.3)
14.3.3.1.5	FAS	Treatment-Emergent Dose Limiting Toxicities by System Organ Class and Preferred Term	Repeat (14.3.3.1.3)
14.3.3.2.1	FAS	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and Severity	Unique
14.3.3.3.1	FAS	Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Repeat (14.3.3.1.3)
14.3.3.3.2	FAS	Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and Severity	Repeat (14.3.3.2.1)
14.3.3.4.1	FAS	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Repeat (14.3.3.1.3)
14.3.3.4.2	FAS	Drug-Related Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Repeat (14.3.3.1.3)
14.3.3.5.1	FAS	Treatment-Emergent Adverse Events Resulting On-Study Deaths by Preferred Term	Repeat (14.3.3.1.3)
14.3.3.5.2	FAS	Deaths Within 28 Days	Unique
14.3.3.6.1	FAS	Treatment-Emergent Adverse Events Leading to Premature Study Drug Discontinuation by Preferred Term	Repeat (14.3.3.1.3)
14.3.4.1.1.1	FAS	Summary of Hematology Laboratory Results by Study Visit	unique
14.3.4.1.1.2	FAS	Hematology: Shift from Baseline	unique
14.3.4.1.2.1	FAS	Summary of Serum Chemistry Laboratory Results by Study Visit	Repeat (14.3.4.1.1.1)
14.3.4.1.2.2	FAS	Serum Chemistry: Shift from Baseline	Repeat (14.3.4.1.1.2)
14.3.4.1.3.1	FAS	Female Reproductive Hormones Laboratory Results by Study Visit	Repeat (14.3.4.1.1.1)
14.3.4.1.3.3	FAS	Female Reproductive Hormones: Shift from Baseline	Repeat (14.3.4.1.1.2)
14.3.4.1.3.2	FAS	Male Reproductive Hormones Laboratory Results by Study Visit	Repeat (14.3.4.1.1.1)
14.3.4.1.3.4	FAS	Male Reproductive Hormones: Shift from Baseline	Repeat (14.3.4.1.1.2)

Table Number	Analysis Set	Table Title/Summary	Type
14.3.4.1.4.1	FAS	Quantitative Urinalysis Laboratory Results by Study Visit	Repeat (14.3.4.1.1.1)
14.3.4.1.4.2	FAS	Qualitative Urinalysis Laboratory Results by Study Visit	unique
14.3.5.1	FAS	Vital Signs: Diastolic Blood Pressure	Repeat (14.3.4.1.1.1)
14.3.5.2	FAS	Vital Signs: Systolic Blood Pressure	Repeat (14.3.4.1.1.1)
14.3.5.3	FAS	Vital Signs: Heart Rate	Repeat (14.3.4.1.1.1)
14.3.5.4	FAS	Vital Signs: Weight	Repeat (14.3.4.1.1.1)
14.3.6.1	FAS	Summary of Concomitant Medications	Repeat
14.3.6.2	FAS	Summary of Concomitant Steroid Therapies	Repeat
14.3.6.3	FAS	Summary of Concomitant Steroid Therapies by Total Daily Dose	Unique
14.3.7.1.1	FAS	Electrocardiogram Summary: HR	Repeat (14.3.4.1.1.1)
14.3.7.1.2	FAS	Electrocardiogram Summary: PR	Repeat (14.3.4.1.1.1)
14.3.7.1.3	FAS	Electrocardiogram Summary: QRS	Repeat (14.3.4.1.1.1)
14.3.7.1.4	FAS	Electrocardiogram Summary: QT	Repeat (14.3.4.1.1.1)
14.3.7.1.5	FAS	Electrocardiogram Summary: QTcF	Repeat (14.3.4.1.1.1)
14.3.8.1.1	FAS Males with Ultrasound	Summary of Testicular Adrenal Rest Tumour (TART) (from Ultrasound) by Study Visit and Cohort	unique
14.3.8.2.1	FAS	Summary of Beck Depression Index-II (BDI-II) Total Score by Study Visit	Unique
14.3.8.2.2	FAS	Shift Table of Beck Depression Index-II (BDI-II) Total Score by Study Visit	unique

Table Number	Analysis Set	Table Title/Summary	Type
14.3.8.3.1	FAS	Summary of Columbia-Suicide Severity Rating Scale (C-SSRS)	Unique
14.3.8.4.1	FAS	Summary of Hospital Anxiety and Depression Scale (HADS) by Study Visit and Cohort	Repeat (14.3.4.1.1.1)

13.5. Efficacy Figures

Figure Number	Analysis Set	Type	Title	Notes		
				x-axis	Legend	
15.1.1.1	PD	SER	Serum 17-OHP Percent Change (95%CI) from Baseline at Week 2 (8 am) Note: derived from GMR	Total Daily Dose (0,200,400,600,1000)		unique
15.1.1.2	PD	SER	Serum 17-OHP Percent Change (95%CI) from Baseline at Week 2 (6/8 am) Note: derived from GMR	Total Daily Dose (0,200,400,600,1000)		Repeat
15.1.2	PD	SER	Serum 17-OHP Percent Change (95%CI) from Baseline at Week 2 (AUC10pm-10am; PM Period) Note: derived from GMR	Total Daily Dose (0,200,400,600,1000)		Repeat
15.1.3.1	PD	SER	Serum 17-OHP Percent Change from Predose by timepoint At Week 2 PM Period	Time (10pm,2am,3am,4am,6am,8am,10am)	Day -1, 100BID, 200BID, 200QD, 600QD,1000QD	Unique
15.1.3.2	PD	SER	Serum 17-OHP Percent Change from Predose by timepoint At Week 2: 24hour Period	Time (10am, 12pm,1pm,2pm,3pm,4pm,5pm,6pm,8pm, 10pm,2am,3am,4am,6am,8am,10am)	Day -1, 100BID, 200BID,	Unique
15.1.4.1	PD	forest	Serum 17-OHP Geometric Mean Ratio (95% CI) by Dose at Week 2: AUC10pm-10am; PM Period	Geometric Mean (95% CI) Change from Predose	100BID, 200BID, 200QD, 600QD,1000QD	Unique
15.1.4.2	PD	forest	Serum 17-OHP Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: AUC10am-10pm; 24 hour Period	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID,	Repeat

Figure Number	Analysis Set	Type	Title	Notes		
				x-axis	Legend	
15.1.4.3	PD	forest	Serum 17-OHP Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: AUC10am-10pm; AM Period	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID,	Repeat
15.1.4.4	PD	forest	Serum 17-OHP Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: 8 am	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID, 200QD, 600QD,1000QD	Repeat
15.1.4.5	PD	forest	Serum 17-OHP Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: average 6/8 am	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID, 200QD, 600QD,1000QD	repeat
15.1.5.1	PD	WF	Serum 17-OHP By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 100mg BID)	Subjects		Unique
15.1.5.2	PD	WF	Serum 17-OHP By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 200mg BID)	Subjects		repeat
15.1.5.3	PD	WF	Serum 17-OHP By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 200mg QD)	Subjects		repeat
15.1.5.4	PD	WF	Serum 17-OHP By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 600mg QD)	Subjects		repeat
15.1.5.5	PD	WF	Serum 17-OHP By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 1000mg QD)	Subjects		repeat
15.1.6.1	PD	WF	Serum 17-OHP By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 100mg BID)	Subjects		repeat
15.1.6.2	PD	WF	Serum 17-OHP By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 200mg BID)	Subjects		repeat

Figure Number	Analysis Set	Type	Title	Notes		
				x-axis	Legend	
15.1.6.3	PD	WF	Serum 17-OHP By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 200mg QD)	Subjects		repeat
15.1.6.4	PD	WF	Serum 17-OHP By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 600mg QD)	Subjects		repeat
15.1.6.5	PD	WF	Serum 17-OHP By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 1000mg QD)	Subjects		repeat
15.2.1.1	PD	SER	Serum ACTH Percent Change (95%CI) from Baseline at Week 2 (8 am) Note: derived from GMR	Total Daily Dose (0,200,400,600,1000)		unique
15.2.1.2	PD	SER	Serum ACTH Percent Change (95%CI) from Baseline at Week 2 (6/8 am) Note: derived from GMR	Total Daily Dose (0,200,400,600,1000)		Repeat
15.2.2	PD	SER	Serum ACTH Percent Change (95%CI) from Baseline at Week 2 (AUC10pm-10am; PM Period) Note: derived from GMR	Total Daily Dose (0,200,400,600,1000)		Repeat
15.2.3.1	PD	SER	Serum ACTH Percent Change from Predose by timepoint At Week 2 PM Period	Time (10pm,2am,3am,4am,6am,8am,10am)	Day -1, 100BID, 200BID, 200QD, 600QD,1000QD	Repeat
15.2.3.2	PD	SER	Serum ACTH Percent Change from Predose by timepoint At Week 2: 24hour Period	Time (10am, 12pm,1pm,2pm,3pm,4pm,5pm,6pm,8pm, 10pm,2am,3am,4am,6am,8am,10am)	Day -1, 100BID, 200BID,	Repeat
15.2.4.1	PD	forest	Serum ACTH Geometric Mean Ratio (95% CI) by Dose at Week 2: AUC10pm-10am; PM Period	Geometric Mean (95% CI) Change from Predose	100BID, 200BID, 200QD, 600QD,1000QD	Repeat

Figure Number	Analysis Set	Type	Title	Notes		
				x-axis	Legend	
15.2.4.2	PD	forest	Serum ACTH Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: AUC10am-10pm; 24 hour Period	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID,	Repeat
15.2.4.3	PD	forest	Serum ACTH Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: AUC10am-10pm; AM Period	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID,	Repeat
15.2.4.4	PD	forest	Serum ACTH Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: 8 am	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID, 200QD, 600QD,1000QD	Repeat
15.2.4.5	PD	forest	Serum ACTH Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: average 6/8 am	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID, 200QD, 600QD,1000QD	Repeat
15.2.5.1	PD	WF	Serum ACTH By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 100mg BID)	Subjects		Repeat
15.2.5.2	PD	WF	Serum ACTH By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 200mg BID)	Subjects		Repeat
15.2.5.3	PD	WF	Serum ACTH By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 200mg QD)	Subjects		Repeat
15.2.5.4	PD	WF	Serum ACTH By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 600mg QD)	Subjects		Repeat
15.2.5.5	PD	WF	Serum ACTH By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 1000mg QD)	Subjects		Repeat
15.2.6.1	PD	WF	Serum ACTH By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 100mg BID)	Subjects		Repeat
15.2.6.2	PD	WF	Serum ACTH By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 200mg BID)	Subjects		Repeat
15.2.6.3	PD	WF	Serum ACTH By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 200mg QD)	Subjects		Repeat

Figure Number	Analysis Set	Type	Title	Notes		
				x-axis	Legend	
15.2.6.4	PD	WF	Serum ACTH By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 600mg QD)	Subjects		Repeat
15.2.6.5	PD	WF	Serum ACTH By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 1000mg QD)	Subjects		Repeat
15.3.1.1	PD	SER	Serum Androstenedione Percent Change (95%CI) from Baseline at Week 2 (8 am) Note: derived from GMR	Total Daily Dose (0,200,400,600,1000)		Repeat
15.3.1.2	PD	SER	Serum Androstenedione Percent Change (95%CI) from Baseline at Week 2 (6/8 am) Note: derived from GMR	Total Daily Dose (0,200,400,600,1000)		Repeat
15.3.4.4	PD	forest	Serum Androstenedione Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: 8 am	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID, 200QD, 600QD,1000QD	Repeat
15.3.4.5	PD	forest	Serum Androstenedione Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: average 6/8 am	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID, 200QD, 600QD,1000QD	Repeat
15.3.5.1	PD	WF	Serum Androstenedione By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 100mg BID)	Subjects		Repeat
15.3.5.2	PD	WF	Serum Androstenedione By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 200mg BID)	Subjects		Repeat
15.3.5.3	PD	WF	Serum Androstenedione By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 200mg QD)	Subjects		Repeat
15.3.5.4	PD	WF	Serum Androstenedione By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 600mg QD)	Subjects		Repeat

Figure Number	Analysis Set	Type	Title	Notes		
				x-axis	Legend	
15.3.5.5	PD	WF	Serum Androstenedione By Subject Waterfall Plot of Percent Change from Baseline 8am (SPR001 1000mg QD)	Subjects		Repeat
15.3.6.1	PD	WF	Serum Androstenedione By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 100mg BID)	Subjects		Repeat
15.3.6.2	PD	WF	Serum Androstenedione By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 200mg BID)	Subjects		Repeat
15.3.6.3	PD	WF	Serum Androstenedione By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 200mg QD)	Subjects		Repeat
15.3.6.4	PD	WF	Serum Androstenedione By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 600mg QD)	Subjects		Repeat
15.3.6.5	PD	WF	Serum Androstenedione By Subject Waterfall Plot of Percent Change from Baseline 6/8am (SPR001 1000mg QD)	Subjects		Repeat
15.4.1.1	PD	SER	Testosterone Percent Change (95%CI) from Baseline at Week 2 (8 am) Note: derived from GMR	Total Daily Dose (0,200,400,600,1000)		Repeat
15.4.1.2	PD	SER	Testosterone Percent Change (95%CI) from Baseline at Week 2 (6/8 am) Note: derived from GMR	Total Daily Dose (0,200,400,600,1000)		Repeat
15.4.3.1	PD	SER	Testosterone Percent Change from Predose by timepoint At Week 2 PM Period	Time (10pm,2am,3am,4am,6am,8am,10am)	Day -1, 100BID, 200BID, 200QD, 600QD,1000QD	Repeat

Figure Number	Analysis Set	Type	Title	Notes		
				x-axis	Legend	
15.4.3.2	PD	SER	Testosterone Percent Change from Predose by timepoint At Week 2: 24hour Period	Time (10am, 12pm,1pm,2pm,3pm,4pm,5pm,6pm,8pm, 10pm,2am,3am,4am,6am,8am,10am)	Day -1, 100BID, 200BID,	Repeat
15.4.4.4	PD	forest	Testosterone Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: 8 am	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID, 200QD, 600QD,1000QD	Repeat
15.4.4.5	PD	forest	Testosterone Geometric Mean (95% CI) Change from Baseline by Dose at Week 2: average 6/8 am	Geometric Mean (95% CI) Change from Baseline	100BID, 200BID, 200QD, 600QD,1000QD	Repeat
15.5.3.1	PD	SER	Cortisol Percent Change from Predose by timepoint At Week 2 PM Period	Time (10pm,2am,3am,4am,6am,8am,10am)	Day -1, 100BID, 200BID, 200QD, 600QD,1000QD	Repeat
15.5.4.1	PD	forest	Cortisol 17-OHP Geometric Mean Ratio (95% CI) by Dose at Week 2: AUC10pm-10am; PM Period	Geometric Mean (95% CI) Change from Predose	100BID, 200BID, 200QD, 600QD,1000QD	Repeat
15.6.1.1	PD	SER	Mean ± SE Observed Value in Salivary Pharmacodynamic Biomarkers over Time by Planned Dose Level/Visit, and Cohort	Total Daily Dose (0,200,400,600,1000)		Repeat
15.6.1.2	PD	SER	Mean ± SE Percent Change from Baseline in Salivary Pharmacodynamic Biomarkers over Time by Planned Dose Level/Visit, and Cohort	Total Daily Dose (0,200,400,600,1000)		Repeat
15.6.1.3	PD	SER	Mean ± SE Change from Baseline in Salivary Pharmacodynamic Biomarkers over Time by Planned Dose Level/Visit, and Cohort	Total Daily Dose (0,200,400,600,1000)		Repeat
15.6.1.4	PD	SER	Individual Pharmacodynamic Biomarkers by Sex, Planned Dose Level, and Cohort	Total Daily Dose (0,200,400,600,1000)	Subject	Repeat

13.6. Pharmacokinetic/Pharmacodynamic Data

Table Number	Analysis Set	Table Title/Summary	Type
Table 14.4.1.1	PK	Summary of SPR001 Concentrations (unit) Over Time by Actual Dose Level	Unique
Figure 14.4.1.2.1	PK	Mean SPR001 Pharmacokinetic Concentrations Over Time by Actual Dose Level, Linear Scale	Unique
Figure 14.4.1.2.2	PK	Mean SPR001 Pharmacokinetic Concentrations Over Time by Actual Dose Level, Semi-logarithmic Scale	Repeat
Figure 14.4.1.2.3	PK	SPR001 Pharmacokinetic Concentrations Over Time by Subject and Actual Dose Level, Linear Scale	Repeat
Figure 14.4.1.2.4	PK	SPR001 Pharmacokinetic Concentrations Over Time by Subject and Actual Dose Level, Semi-logarithmic Scale	Repeat
Table 14.4.1.3	PK	Summary of SPR001 Pharmacokinetic Parameters by Actual Dose Level	Repeat
Figure 14.4.3.1.1.1	PK/PD	Plot of Observed SPR001 Concentrations vs Observed Serum 17-OHP Concentrations	Unique
Figure 14.4.3.1.1.2	PK/PD	Plot of Mean SPR001 Concentrations vs Change from Predose as Baseline in ACTH Concentrations	Repeat
Figure 14.4.3.1.2.1	PK/PD	Plot of Observed SPR001 Concentrations vs Observed ACTH Concentrations	Repeat
Figure 14.4.3.1.2.2	PK/PD	Plot of Mean SPR001 Concentrations vs Change from Time-Matched Baseline in Androstenedione Concentrations	Repeat
Figure 14.4.3.1.3.1	PK/PD	Plot of Observed SPR001 Concentrations vs Observed Androstenedione Concentrations	Repeat
Figure 14.4.3.1.3.2	PK/PD	Plot of Mean SPR001 Concentrations vs Change from Time-Matched Baseline in Testosterone Concentrations	Repeat

Figure 14.4.3.1.4.1	PK/PD	Plot of Observed SPR001 Concentrations vs Observed Testosterone Concentrations	Repeat
Figure 14.4.3.1.4.2	PK/PD	Plot of Mean SPR001 AUC vs Change from Baseline in Serum 17-OHP AUC	Repeat
Figure 14.4.3.2.2	PK/PD	Correlations between SPR001 Avg_{6a-8a} (unit) and Change from Baseline in Serum 17-OHP Avg_{6a-8a} (unit) by Planned Dose Level	Unique
Table 14.4.3.2.3	PK/PD	Plot of Mean SPR001 Avg_{6a-8a} vs Change from Baseline in Serum 17-OHP Avg_{6a-8a}	Repeat
Figure 14.4.3.2.4	PK/PD	Correlations between SPR001 AUC (10pm-8am; PM Period) and Change from Baseline in ACTH AUC (10pm-8am; PM Period) by Planned Dose Level	Repeat
Table 14.4.3.3.1	PK/PD	Plot of Mean SPR001 AUC (10pm-8am; PM Period) vs Change from Baseline in ACTH AUC (10pm-8am; PM Period)	Repeat
Figure 14.4.3.3.2	PK/PD	Correlations between SPR001 Avg_{6a-8a} (unit) and Change from Baseline in ACTH Avg_{6a-8a} (unit) by Planned Dose Level	Repeat
Table 14.4.3.3.3	PK/PD	Plot of Mean SPR001 Avg_{6a-8a} vs Change from Baseline in ACTH Avg_{6a-8a}	Repeat
Figure 14.4.3.3.4	PK/PD	Correlations between SPR001 Avg_{6a-8a} (unit) and Change from Baseline in Androstenedione Avg_{6a-8a} (unit) by Planned Dose Level	Repeat
Table 14.4.3.4.1	PK/PD	Plot of Mean SPR001 Avg_{6a-8a} vs Change from Baseline in Androstenedione Avg_{6a-8a}	Repeat
Figure 14.4.3.4.2	PK/PD	Correlations between SPR001 Avg_{6a-8a} (unit) and Change from Baseline in Testosterone Avg_{6a-8a} (unit) by Planned Dose Level	Repeat
Table 14.4.3.5.1	PK/PD	Plot of Mean SPR001 Avg_{6a-8a} vs Change from Baseline in Testosterone Avg_{6a-8a}	Repeat

13.7. Corticosteroid Analyte Data

Table Number	Analysis Set	Table Title/Summary	Type
Table 14.4.3.6.1.1	PD – Subjects on Corticosteroids	Summary of Corticosteroid Analyte AUC (10 pm-8 am; PM period)	Repeat
Table 14.4.3.6.1.2	PD – Subjects on Corticosteroids	Summary of Corticosteroid Analyte AUC (10am-10am; 24 hour)	Repeat
Table 14.4.3.6.1.3	PD – Subjects on Corticosteroids	Summary of Corticosteroid Analyte AUC (10am-10pm; AM period)	Repeat
Table 14.4.3.6.2.1	PD – Subjects on Corticosteroids	Summary of Corticosteroid Analyte Concentrations with Predose as Baseline by Time Point	Repeat
Table 14.4.3.6.2.2	PD – Subjects on Corticosteroids	Summary of Time-Matched Corticosteroid Analyte Average (6-8 am)	Repeat
Table 14.4.3.6.3.3	PD – Subjects on Corticosteroids	Summary of Corticosteroid Analyte Concentrations by Time Point	Repeat

Figure Number	Analysis Set	Type	Title	Notes		Type
				x-axis	Legend	
Figure 14.4.3.6.1	PD – Subjects on Corticosteroids	Forest	Serum Corticosteroid Analyte Geometric Mean Ratio (95% CI) by Dose at Week 2: AUC10pm-8am; PM Period	Geometric Mean Ratio (95% CI)	Total Daily Dose (100BID, 200BID, 200QD, 600QD,1000QD)	Repeat
Figure 14.4.3.6.2	PD – Subjects on Corticosteroids	Forest	Serum Corticosteroid Analyte Geometric Mean Ratio (95% CI) by Dose at Week 2: AUC10am-10am; 24 hour Period	Geometric Mean Ratio (95% CI)	Total Daily Dose (100BID, 200BID)	Repeat

Figure Number	Analysis Set	Type	Title	Notes		Type
				x-axis	Legend	
Figure 14.4.3.6.3	PD – Subjects on Corticosteroids	Forest	Serum Corticosteroid Analyte Geometric Mean Ratio (95% CI) by Dose at Week 2: AUC10am-10pm; AM Period	Geometric Mean Ratio (95% CI)	Total Daily Dose (100BID, 200BID)	Repeat
Figure 14.4.3.7.1	PD – Subjects on Corticosteroids	SER	Serum Corticosteroid Analyte Percent Change (95%CI) from Baseline at Week 2 (8 am) Note: derived from GMR	Total Daily Dose (100BID, 200BID, 200QD, 600QD,1000QD)		Repeat
Figure 14.4.3.7.2	PD – Subjects on Corticosteroids	SER	Serum Corticosteroid Analyte Percent Change (95%CI) from Baseline at Week 2 (6/8 am) Note: derived from GMR	Total Daily Dose (100BID, 200BID, 200QD, 600QD,1000QD)		Unique
Figure 14.4.3.8.1	PD – Subjects on Corticosteroids	WF	Serum Corticosteroid Analyte By Subject Waterfall Plot of Percent Change from Baseline 8am by Dose		Subject	Repeat
Figure 14.4.3.8.2	PD – Subjects on Corticosteroids	WF	Serum Corticosteroid Analyte By Subject Waterfall Plot of Percent Change from Baseline in AUC10pm-8am; PM Period by Dose		Subject	Repeat
Figure 14.4.3.8.3	PD – Subjects on Corticosteroids	WF	Serum Corticosteroid Analyte By Subject Waterfall Plot of Percent Change from Baseline in AUC10am-10am; 24 hour Period by Dose		Subject	Repeat
Figure 14.4.3.8.4	PD – Subjects on Corticosteroids	WF	Serum Corticosteroid Analyte By Subject Waterfall Plot of Percent Change from Baseline in AUC10am-10pm; AM Period by Dose		Subject	Repeat

13.8. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number SPR001-201.

In general, one listing will be produced per CRF domain. All listings will be sorted by and subject number and dose level. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Listing Number	Population	Table Title / Summary
16.2.1.1	All Subjects	Subject Disposition
16.2.1.2	FAS	Discontinuations
16.2.1.3	All Subjects	Inclusion and Exclusion Criteria Not Met
16.2.1.4	Screen Failures	Screen Failures
16.2.2.1	All Subjects	Protocol Deviations
16.2.2.2	All Subjects	Analysis Populations
16.2.3.1	FAS	Subjects excluded from Efficacy analyses
16.2.4.1	All Subjects	Demographics and Baseline Information
16.2.4.2	All Subjects	Medical History
16.2.4.3	All Subjects	Mini International Neuropsychiatric Interview (MINI)
16.2.4.4	All Subjects	Prior Corticosteroid Therapies
16.2.4.5	All Subjects	Historical Hormonal Laboratory Data
16.2.5.1	FAS	Study Drug Accountability
16.2.5.2	FAS	Study Medication and Snack Diary
16.2.5.3	FAS	Dose Reduction and Escalation
16.2.5.4	PK	Pharmacokinetic Blood Collection and Concentrations
16.2.5.5	PK	Calculated Pharmacokinetic Parameters

Listing Number	Population	Table Title / Summary
16.2.6.1.1	PD	Pharmacodynamic Blood Collection
16.2.6.1.2	PD	Pharmacodynamic Concentrations
16.2.6.2	PD	Calculated Pharmacodynamic Parameters
16.2.7.1.1	All Subjects	Adverse Events
16.2.7.1.2	All Subjects	Adverse Events of Special Interest
16.2.7.1.3	All Subjects	Adverse Events Triggering Stopping Rules
16.2.7.2	All Subjects	Adverse Events leading to Discontinuation
16.2.7.3	All Subjects	Serious Adverse Events
16.2.7.4	All Subjects	Listing of Deaths
16.2.8.1	All Subjects	Clinical Laboratory Data: Serum Chemistry
16.2.8.2	All Subjects	Clinical Laboratory Data: Hematology
16.2.8.3	All Subjects	Clinical Laboratory Data: Reproductive Hormones
16.2.8.4	All Subjects	Clinical Laboratory Data: Urinalysis
16.2.8.5	All Subjects	Clinical Laboratory Data: Serology
16.2.8.6	All Subjects	Clinical Laboratory Data: Other
16.2.8.7	All Subjects	Liver Function Tests
16.2.9.1	All Subjects	Vitals Signs
16.2.9.2	All Female Subjects	Physical Examinations: Females
16.2.9.3	All Male Subjects	Physical Examinations: Males
16.2.10.1	All Subjects	Prior and Concomitant Medications
16.2.10.2	All Subjects	Prior and Concomitant Steroid Therapies
16.2.11.1	All Subjects	12-Lead Electrocardiograms
16.2.12.1	All Male Subjects with Ultrasound	Testicular Ultrasound
16.2.12.2	All Subjects	Beck Depression Index-II (BDI-II)

Listing Number	Population	Table Title / Summary
16.2.12.3	All Subjects	Columbia-Suicide Severity Rating Scale (C-SSRS)
16.2.12.4	All Subjects	SF-36 (Acute Form)
16.2.12.5	All Subjects	PGIC
16.2.12.6	All Subjects	Hospital Anxiety and Depression Scale
16.2.12.7	All Subjects	CAH signs and symptoms interview

Appendix 1: Library of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
AD	associated documents
ADR	adverse drug reactions
AE	adverse event
AESI	adverse events special interest
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BLQ	beneath limit of quantification
BMI	body mass index
BRD	business requirements document
BSL	biostatistician lead
CCGs	CRF completion guidelines
CD	compact disc
CDISC	clinical data interchange standards consortium
CEC	central ethics committee
CFR	code of federal regulations
CI	confidence intervals
CIOMS	council for international organizations of medical sciences

Abbreviation	Definition
CIP	clinical investigational plan
CM	clinical manager
CMP	clinical monitoring plan
COV	close out visit
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSM	clinical supply manager
CSR	clinical study report
CTA	clinical trial administrator
CTM	clinical trial manager
CTMS	clinical trial management system
DB	database
DBL	database lock
DBP	diastolic blood pressure
DCRF	data change request form
DDE	drug dispensing error form
DEA	drug enforcement administration

Abbreviation	Definition
DEX	dexamethasone
DIA	drug information association
DIS	data integration specification
DLT	dose limiting toxicity
DM	data management
DMB	data monitoring board
DMC	data monitoring committee
DML	data management lead
DMP	data management plan
DNA	deoxyribonucleic acid
DOB	date of birth
DS	document specialist
DSG	drug safety group
DSM	drug supply management (drug distributor)
DSMB	data safety monitoring board
DSP	data safety plan
DSUR	development safety update report
DTS	data transfer specification
DVD	digital video disk

Abbreviation	Definition
EC	ethics committee
ECD	edit check and derivation specifications
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European medicines agency
eTMF	electronic trial master file
EU	European Union
FA	full analysis
FDA	food and drug administration
FMP	file management plan
FPFV	first patient first visit
FPI	first patient in
GCP	good clinical practice
GMP	good manufacturing practices
GPV	global pharmacovigilance
HR	heart rate
IB	investigator's brochure
IC or ICF	informed consent or informed consent form

Abbreviation	Definition
ICH	international council for harmonization
ID	identification
IDM	independent drug monitoring
IEC	independent ethics committee
IM	investigator meeting
IMV	interim monitoring visit
IND	investigational new drug
INDSR	investigational new drug safety reports
IP	investigational product
IRB	institutional review board
IRF	inventory release file
IRR	infusion related reactions
IRT	interactive response technology
ISF	investigator site file
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
IxRS	interactive voice/web response system
KPI	key performance indicator

Abbreviation	Definition
LAN	local area network
LDM	lead data manager
LMS	learning management system
LLOQ	lower limit of quantification
LPI	last patient in
LPLV	last patient last visit
LPO	last patient out
MAAP	medical affairs and pharmacovigilance teams
MAH	marketing authorization holder
MedDRA	medical dictionary for regulatory activities
MHRA	medicines and healthcare products regulatory agency
MM	medical monitor
MMP	medical monitoring plan
MMRM	mixed effect model repeat measurement
MTD	maximum tolerated dose
MVR	monitoring visit report
N	number
NA	not applicable
NCS	non-clinically significant

Abbreviation	Definition
NF	non-functional
PD	protocol deviation
PDGP	protocol deviation guidance plan
PE	physical examination
PI	principal investigator
PIN	personal identification number
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PM	project manager
PMP	project management plan
PP	per-protocol
PRIMS	Premier Research information management system
PS	project specialist
PV	pharmacovigilance
PVG	pharmacovigilance group
QA	quality assurance
QARC	quality assurance, risk and compliance
QC	quality control
QOL	quality of life

Abbreviation	Definition
ROT	record of training
RR	respiratory rate or relative rate
RSM	regional site monitor
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure
SC	study coordinator
SCR	software change request
SD	standard deviation
SDS	study design specifications
SDTM	study data tabulation model
SDV	source data verification
SECC	self-evident correction conventions
SECP	self-evident correction plan
SF	screen failure
SFT or SFTP	secure file transfer or secure file transfer plan
SIV	site initiation visit
SLA	service level agreement

Abbreviation	Definition
SMP	safety management plan
SOC	system organ class
SOP	standard operating procedure
SOW	statement of work
SQV	site qualification visit
SUA	start-up associate
SUSAR	suspected, unexpected, serious adverse (drug) reaction
TA	trial assistant
TEAE	treatment-emergent adverse event
TMF	trial master file
TOM	task ownership matrix
UAT	user acceptance testing
USA	United States of America
UTC	universal coordinated time
WAN	wide area network
WAR	work at risk
WG	working guideline
WHO	world health organization
WHO-DD	world health organization drug dictionary