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STATISTICAL ANALYSIS PLAN
PHASE 2

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STUDY DRUG:
Crinecerfont (NBI-74788)

PROTOCOL NUMBER:
NBI-74788-CAH2008

STUDY TITLE:
A Phase 2, Open-Label, Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of NBI-74788 in Pediatric Subjects with Congenital Adrenal Hyperplasia

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

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

17-OHP	17-hydroxyprogesterone
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
AUC_{0-12}	AUC from 0 to 12 hours
BMI	Body mass index
BPRS-C	Brief Psychiatric Rating Scale for Children
BSA	Body surface area
CAH	Congenital adrenal hyperplasia
C_{avg}	Average plasma concentration at steady state
CL/F	Apparent systemic clearance after oral administration
C_{max}	Maximum plasma concentration
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale, Children's Version
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
GGT	Gamma-glutamyl transferase
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPD	Important protocol deviation
λz	Apparent terminal rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NBI	Neurocrine Biosciences, Inc.
PD	Pharmacodynamic(s)

PK	Pharmacokinetic(s)
PT	Preferred term
QTcF	Corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SOC	System organ class
TEAE	Treatment-emergent adverse event
$t_{1/2}$	Terminal half life
t_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays that will be prepared to summarize the data from the Phase 2 study described in Neurocrine Biosciences, Inc. (NBI) Protocol NBI-74788-CAH2008.

This SAP was developed in accordance with ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) E9 guidance. All decisions regarding the final analysis, as defined in this SAP document, will be made prior to database lock. Changes made to the planned analyses after finalization of this SAP and database lock will be described in the clinical study report (CSR). Further information related to study design and methodology can be found in the protocol.

3. STUDY OBJECTIVES

3.1. Study Objectives

The objectives of the study are as follows:

- To assess the safety and tolerability of crinecerfont (NBI-74788) in pediatric subjects 14 to 17 years of age with congenital adrenal hyperplasia (CAH).
- To evaluate the effect of repeated doses of crinecerfont on endogenous levels of pharmacodynamic (PD) biomarkers in pediatric subjects with CAH.
- To evaluate the pharmacokinetics (PK) of crinecerfont and metabolites in pediatric subjects with CAH.

4. STUDY DESIGN

4.1. Summary of Study Design

This is a Phase 2, open-label, multiple-dose study to assess the safety, tolerability, PK, and PD of crinecerfont in approximately 12 pediatric female and male subjects (14 to 17 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH. Crinecerfont 50 mg bid will be administered for 14 consecutive days with breakfast and evening meals beginning on the evening of Day 1.

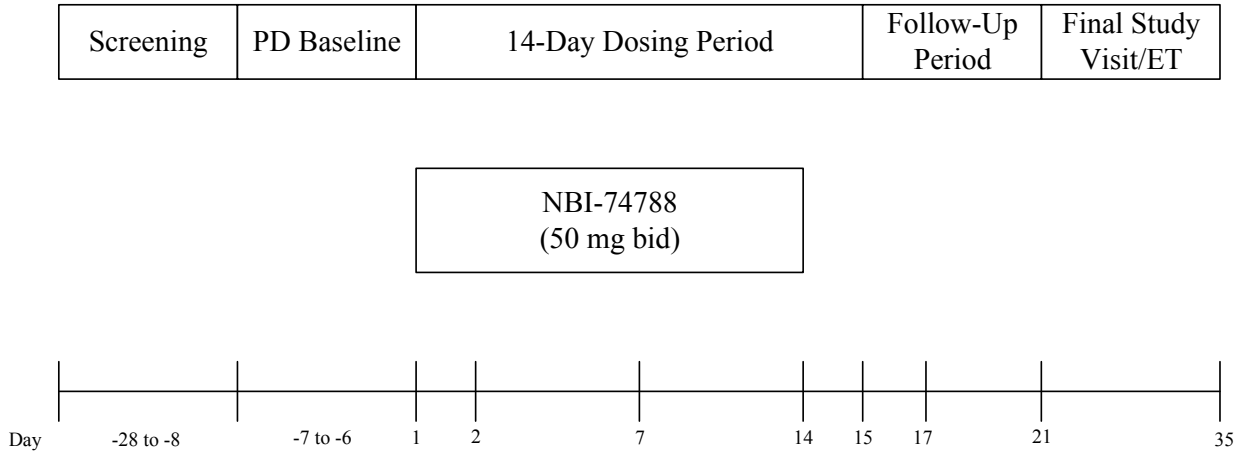
Eligible subjects who have a screening 17-OHP level ≥800 ng/dL will be admitted to the study center on Day -7 for 1 night and have baseline serial PD samples collected over a 24-hour period beginning that evening. Baseline serial PD samples will be collected at approximately 1845, 2000, 2300, 0100, 0300, 0700, 1000, 1500, and 1900 hours.

The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

Subjects will be admitted to the study center on Days 1 and 14 (first and last day of dosing). The first dose of study drug, crinecerfont 50 mg, will be administered at approximately 1900 hours with subjects' evening meal on Day 1. Study drug will be administered at the study center on Days 2 and 14 with subjects' breakfast and evening meals, respectively. The subjects' usual morning dose of concurrent steroidal treatments, study drug dosing, and breakfast (snacks will be allowed prior to breakfast) will be delayed until after the 15-hour postdose PD samples are collected (ie, at approximately 1000 hours) on Day 2. The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 15-hour postdose PD samples are collected (ie, at approximately 1000 hours) on Day 15. Study drug will be self-administered at home under parent/guardian supervision at approximately 0700 hours (with breakfast) and 1900 hours (with evening meal) on Days 3 to 13.

The study design schematic is shown in Figure 1.

Figure 1: Study Design Schematic



bid=twice daily; ET=early termination; PD=pharmacodynamic; NBI-74788=crinecerfont.

4.2. Sample Size Considerations

The sample size for this study is based on practical clinical considerations with no formal statistical power calculations.

4.3. Clinical Assessments

Pharmacodynamic assessments include:

- [redacted] Morning 17-OHP (serum; ng/dL) from the 12- and 15-hour postdose samples (collected at 0700 and 1000 hours).
- [redacted] 17-OHP at all other times, androstenedione (serum; ng/dL), testosterone (serum; ng/dL), cortisol (serum; µg/dL), and adrenocorticotropic hormone (ACTH; plasma; pg/mL).

Pharmacokinetic assessments include:

The following plasma PK parameters will be calculated for crinecerfont and metabolites for the Day 1 to 2 and the Day 14 to 15 sampling intervals:

- Area under the plasma concentration versus time curve from 0 to 12 hours ($AUC_{0–12}$).
- Observed maximum plasma concentration (C_{max}).
- Time to C_{max} (t_{max}).

Additional PK parameters for Days 14 to 15 only:

- Average plasma concentration at steady state (C_{avg}).
- Percent fluctuation at steady state (%fluctuation).
- Accumulation ratio at steady state.
- Apparent terminal half-life ($t_{½}$).
- Apparent terminal rate constant (λz).
- Apparent mean residence time (MRT).
- Apparent systemic clearance after oral administration (CL/F) (crinecerfont only).

Safety assessments include:

- Adverse events (AEs).
- Clinical laboratory tests (clinical chemistry, hematology, [redacted] and urinalysis).
- Vital signs.
- Physical examinations (including musculoskeletal exam).
- 12-lead electrocardiograms (ECGs).
- Columbia-Suicide Severity Rating Scale (C-SSRS), Children's Version

- Brief Psychiatric Rating Scale for Children (BPRS-C).

See Table 2 of the study protocol for a complete schedule of assessments.

5. PLANNED ANALYSES

5.1. Interim Analyses

No interim analysis is planned for this study.

5.2. Final Analyses

Final analyses, as specified in the protocol and in this SAP, will be performed after the study database has been locked.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

All analyses described in this plan are considered *a priori* analyses in that they have been defined prior to locking the study database. Analyses defined subsequent to locking the database will be considered *post hoc* analyses and will be applied as exploratory methodology. Any *post hoc* analyses will be clearly identified in the CSR.

6.1. General Statistical Procedures

Descriptive statistical methods will be used to summarize the data from this study. The term "descriptive statistics" refers to the number of subjects, mean, median, standard deviation (SD) or standard error (SE), minimum, and maximum for continuous and ordinal categorical variables; and refers to the number and percentage of subjects (or events) for categorical variables. Additional descriptive statistics, such as the coefficient of variation (CV), will be presented for selected PK data.

Unless otherwise noted, data will be summarized by a single dose group (crinecerfont 50 mg bid). For the purposes of PD data summaries, serial sampling that starts at the 15 minutes pre-evening dose on Study Day 1 and continues until the 24 hours post-evening dose on Study Day 2 will be referred to as "Day 1"; serial sampling that starts at the 15 minutes pre-evening dose on Study Day 14 and continues until the 24 hours post-evening dose on Study Day 15 will be referred to as "Day 14" in the data summaries.

Summary statistics will be displayed using the following decimal precision rules: the minimum and maximum will have the same number of decimal places as the data; the mean, median, SD, and SE will have one more decimal place than the data being summarized. Percentages will be displayed using one decimal place; percentages for 0 counts will be omitted. These rules may be modified if warranted, based on practical considerations.

6.2. Analysis Sets

6.2.1. Definition of Analysis Sets

6.2.1.1. Safety Analysis Set

The safety analysis set will include all subjects who take at least one dose of study drug and have any postbaseline safety data. The safety analysis set will be used for all summaries of safety data (e.g., AEs, clinical laboratory data) and pharmacokinetic data.

6.2.1.2. Pharmacodynamic Analysis Set

The pharmacodynamic analysis set will include all subjects who take at least one dose of study drug and have at least one PD parameter measurement at PD baseline (Days -7 to -6) and at least one PD parameter measurement at Day 1 or Day 14. The pharmacodynamic analysis set will be used for all summaries of pharmacodynamic data.

6.2.2. Summary of Analysis Sets

A summary of the number and percentage of subjects included in (and excluded from, as applicable) each analysis set will be provided. The number and percentage of subjects excluded from each analysis set by reason for exclusion will also be provided.

6.2.3. Application of Analysis Sets

Summaries of subject disposition, analysis set inclusion/exclusion status, and Important Protocol Deviations (IPDs) will include all enrolled subjects. All other summaries by analysis set are identified in Table 2.

Table 2: Data Summaries by Analysis Set

Data Summary/Analysis	Analysis Set	
	Safety	Pharmacodynamic
Demographics[1]	X	X
Baseline subject characteristics[1]	X	X
CAH history	X	
Pharmacodynamic data		X
Plasma concentrations	X	
PK parameters	X	
Adverse events	X	
Clinical laboratory data	X	
Vital signs	X	
Weight	X	
ECG	X	
C-SSRS, Children's Version	X	
BPRS-C	X	

[1] if the safety analysis set and the pharmacodynamic analysis set are the same, only one set of tables will be created using the safety analysis set.

6.3. Baseline Definitions

6.3.1. Study Baseline

Study baseline will be defined as the last reported value prior to study drug dosing for all safety assessments. The assessments collected at the Day 1 study visit will serve as the baseline value for all assessments. With the exception of C-SSRS, if a Day 1 visit value is not available, then the last measurement collected on or prior to the date of the Day 1 study visit will serve as baseline. C-SSRS values that are missing at Day 1 will remain missing.

6.3.2. Pharmacodynamic Baseline

For all pharmacodynamic data analyses, baseline will be defined as the PD values collected during the 24 hour PD baseline on Days -7 to -6 of the study. The specific timepoints that will be used to represent PD baseline from Days -7 to -6 are further explained in Section 9 of this SAP.

6.4. Derived and Transformed Data

6.4.1. Study Day

Study day is calculated relative to the date of the Day 1 visit. If the date of interest occurs on or after the Day 1 visit, then the study day will be calculated as: date of interest – date of Day 1 visit + 1. If the date of interest occurs prior to the Day 1 visit, then the study day will be calculated as: date of interest – date of Day 1 visit.

6.4.2. Change and Percent Change from Baseline

Change from baseline is calculated as (postbaseline value – baseline value).

Percent change from baseline is calculated as (change from baseline/baseline value * 100).

If either the baseline or postbaseline value is missing, the change from baseline and percent change from baseline will also be missing. The percent change from baseline will also be missing if the baseline value is equal to zero.

6.4.3. Handling of Pharmacodynamic BLQ Data

Pharmacodynamic data with values that are below the limit of quantification (BLQ) will be set equal to the lower limit of quantification (LLQ) unless the value is between two quantifiable measurements, in which case it will be set to missing.

6.4.4. Handling of Early Termination Visit Data

An early termination (ET) visit occurs when a subject discontinues from the study prior to completing the scheduled Day 35 visit. The data collected at ET visits will be included in summary tables and figures if they correspond to a protocol-specified visit or timepoint.

Early termination visit data which are not captured at a protocol-specified visit or timepoint will not be included in by-visit analyses and summaries. They will be included in any analyses that look across all available assessments during the treatment period, including unscheduled visits. They will also be included in any applicable by-subject data listings.

6.5. Handling of Missing Data

6.5.1. Missing Dates

6.5.1.1. Start Dates for Adverse Events and Prior and Concomitant Medications

Missing and incomplete (“partial”) dates for adverse events (AEs) and concomitant medications will be imputed for the purpose of estimating the time of the event or medication usage in relationship to study treatment. Any data listings will display the original dates as reported in the database.

The imputation rules for AE start dates are as follows:

- If the date is completely missing, the date will be imputed as the date of the first dose of study drug;

- If only the day is missing, the date will be imputed as the date of the first dose of study drug if the month and year match the month and year of the first dose of study drug; otherwise, the missing day will be imputed as the first day of the month;
- If both the day and month are missing, the date will be imputed as the date of the first dose of study drug if the date is in the same year as the first dose of study drug; otherwise, the missing day and month will be imputed as 01 January;
- If any of the above imputations result in a start date that is later than an existing (not imputed) end date for the event, the start date will be imputed as the end date.

The imputation rules for concomitant medication start dates are as follows:

- If the date is completely missing, the date will be imputed as 01 January in the year of the subject's screening vital signs assessment;
- If only the day is missing, the date will be imputed as the date of the first dose of study drug if the date is in the same month and year as the first dose of study drug; otherwise, the missing day will be imputed as the first day of the month;
- If both the day and month are missing, the date will be imputed as the date of the first dose of study drug if the date is in the same year as the first dose of study drug; otherwise, the missing day and month will be imputed as 01 January;
- If any of the above imputations result in a start date which is later than an existing (not imputed) medication stop date, the start date will be imputed as the stop date.

7. IMPACT OF COVID-19 PANDEMIC

This section describes analyses and summaries that will be produced to help determine the potential impact of the COVID-19 pandemic on the study conduct/data and additional details regarding how data that is potentially impacted by the COVID-19 pandemic will be handled in the analysis plan. It is in alignment with the guidance put forth by the US Food and Drug Administration (FDA; Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency [March 2020, updated January 2021]) and European Medicines Agency (EMA; Points to consider on implications of Coronavirus disease [COVID-19] on methodological aspects of ongoing clinical trials [March 2020]).

To help understand the impact of the COVID-19 pandemic on the clinical trial data, the following listings will be generated:

- A listing of all subjects affected by the COVID-19 pandemic. The listing will identify subjects who experience at least one of the following situations due to the COVID-19 pandemic (additional situations may be included):
    - Discontinued study treatment or withdrew from study
    - Presumed or confirmed diagnosis of COVID-19
    - Had at least one COVID-19 pandemic-related major protocol deviation
    - Missed at least one study visit or assessment
    - Required at least one assessment to be collected using a method other than what is defined in the protocol (eg, remotely)
    - Had at least one known study drug interruption
- A listing of subjects who discontinued study treatment and/or withdrew from study due to the COVID-19 pandemic, which will include the specific reasons.
- A listing by subject of visits and assessments affected by the COVID-19 pandemic (eg, missing, partial, collected remotely).

Further classification and summaries of protocol deviations related to the COVID-19 pandemic are detailed in Section 8.2. All assessments (eg, C-SSRS, BPRS-C) that are collected remotely will be included in the analysis.

Additional summaries may be generated to address the potential impact of the COVID-19 pandemic on the efficacy and safety data, as needed, based on ongoing data review or during the final analysis of study data.

8. STUDY POPULATION

8.1. Subject Disposition

The summary of subject enrollment and disposition will display the number and percentage of subjects who were enrolled, who completed through Day 14 of study drug dosing, and who completed the study (ie, up to Day 35). The number of subjects who did not complete the study will also be summarized, both overall and according to the reason for early discontinuation.

A listing of lot numbers used in the study will be provided.

8.2. Protocol Deviations

Protocol deviations described in the study-specific Protocol Deviation Plan will be entered into the clinical trial management system. Prior to database lock, all major protocol deviations that have been entered into the clinical trial management system will be exported to a file and integrated into the study data.

IPDs are protocol deviations that might significantly affect the completeness, accuracy and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. An assessment of IPDs will be performed by a committee composed of NBI Clinical Development project team members prior to database lock. This committee will review a listing of all major protocol deviations reported in the study database and determine which deviations are IPDs.

A summary of the number and percentage of subjects with IPDs by deviation category will be provided using all enrolled subjects. The summary will be repeated for the subset of IPDs that are related to the COVID-19 pandemic.

All major protocol deviations will be presented in a data listing and any that are classified as IPDs will be flagged in the listing. Any major PDs related to the COVID-19 pandemic will also be flagged in the listing.

8.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized using descriptive statistics.

Demographics include:

- Age (years)
- Sex
- Ethnicity
- Race
- [redacted]

Baseline subject characteristics include:

- 17-OHP levels at screening
- Body surface area (BSA; calculated using the DuBois formula and height collected at the screening visit and weight collected at the Day 1 visit; m^2)

- Total daily glucocorticoid dose at screening, expressed in hydrocortisone equivalents (mg/day) (See Table 5)
- Total daily glucocorticoid dose at screening, expressed in hydrocortisone equivalents (See Table 5) and adjusted for BSA ($mg/m^2/day$)
- Glucocorticoid type (hydrocortisone alone; prednisone or equivalent with or without hydrocortisone; dexamethasone with or without another glucocorticoid)
- Height (measured at screening; cm)
- Weight (presented in both pounds and kilograms)
- Body mass index (BMI; calculated using height collected at the screening visit and weight collected at the Day 1 visit; kg/m^2)

8.4. CAH History

CAH history will be summarized using descriptive statistics.

CAH history assessments include:

- How the CAH diagnosis was made
- Number of adrenal crises within the past 2 years
- Age at menarche (female subjects only)
- Menstrual cycle frequency (in days; female subjects only)

9. PHARMACODYNAMIC DATA

PD biomarker data include measurements of ACTH, 17-OHP, androstenedione, testosterone, and cortisol. Note that all summaries of testosterone will be stratified by sex. The following sections describe the summaries and analyses of the PD biomarker data.

9.1. Timepoint Summaries

Observed values for the PD biomarker data will be summarized with descriptive statistics by parameter, visit, and timepoint. This summary will also include the changes from PD baseline to postdose values with the same timepoint (eg, change from Day -7/-6, 6 hours post-evening dose to Day 14, 6 hours post-evening dose). Descriptive statistics for the 24 hour average values of the PD parameters at each visit (excluding Day 7 and Day 21) will also be displayed. Figures of mean (+SE) versus time curves will be generated for each parameter by visit. In addition, these data will be displayed as individual subject observed values versus time curves for each parameter by visit.

9.2. Morning Window Summaries

The peak morning period for ACTH, 17-OHP, androstenedione, and testosterone levels is between 0700 and 1000 hours. For the purposes of analysis, this timeframe will be referred to as the "morning window" and includes all PD biomarker measurements (excluding cortisol) taken during this time. Specifically, the morning window timepoints for PD draws are 12- and 15-hours post-evening crinecerfont dose. This group of timepoints will be summarized using the average of the two morning window timepoints at each visit. If only one timepoint is available, this value will be used as the morning window value. If both timepoints are missing, the morning window value for that subject/visit will be reported as missing.

The morning window values will be summarized with descriptive statistics by PD parameter and visit. In addition to the observed values, descriptive statistics will also be generated for the change from PD baseline to Day 1 and from PD baseline to Day 14, as well as the percent change from PD baseline to Day 1 and from PD baseline to Day 14. Percent change from PD baseline to Day 1 and Day 14 for each subject will be presented as waterfall plots by PD parameter.

9.3. Responder Summaries

The PD biomarker data will also be summarized based on responder definitions for ACTH, 17-OHP, androstenedione, and testosterone (female subjects only). The first responder definition will be composed of subjects who have a 50% or greater reduction from PD baseline to Day 14 in the average of their morning window values. The second responder definition will be composed of subjects who have a 50% or greater reduction from PD baseline to Day 14 for at least one timepoint in the morning window period. The frequency and percentage of subjects meeting each of these responder definitions will be summarized by parameter.

Additionally, a responder definition for the ratio of androstenedione to testosterone (A4/T) in male subjects will be composed of male subjects who have an A4/T ratio greater than or equal to 0.5 (based on the average of the morning window values for androstenedione and testosterone) at PD baseline and who achieve an A4/T ratio less than 0.5 (based on the average of the morning

window values for androstenedione and testosterone) at Day 14. The frequency and percentage of male subjects meeting this responder definition will be summarized.

9.4. Pharmacodynamic/Pharmacokinetic Relationship

The relationship between pharmacodynamic and pharmacokinetic data will be depicted graphically. Scatter plots of percent change from PD baseline to Day 14 in the average of morning window values vs. crinecerfont AUC_{0-12} will be generated for ACTH, 17-OHP, and androstenedione. These plots will also be generated for C_{max}.

10. PHARMACOKINETIC DATA

10.1. Plasma Concentrations

Plasma concentrations of crinecerfont and its metabolite, NBI-756179, will be summarized by visit, and nominal (scheduled) timepoint with descriptive statistics, which will include the coefficient of variation (CV [%]), geometric mean, and geometric CV (%). Figures of arithmetic mean (+SD) concentration vs. time curves will be generated by visit (Day 1, Day 14, and Day 14 through Day 35), and timepoint on both the linear and log (base10) scales.

In addition, these data will be displayed as individual subject plasma concentration vs. time curves by visit on both the linear and log (base 10) scales. Actual times from dosing rather than nominal timepoints will be displayed in the by-subject graphs.

All BLQ values (crinecerfont < 5.00 ng/mL; NBI-756179 < 0.500 ng/mL) will be set equal to zero (0) in the plasma concentration summaries, with the exception of the geometric mean and geometric CV (%) which will be treated as missing.

Subjects with significant deviations that could impact the interpretation of study data (eg, missed study drug dosing, emesis) will be excluded from summaries.

10.2. Plasma PK Parameters

The plasma PK parameters listed in Section 4.3 will be summarized with descriptive statistics. These statistics will include the arithmetic mean, SD, median, geometric mean, geometric CV(%), and range for each parameter. PK parameters will be calculated using [redacted].

It should be noted that the handling of BLQ concentration values for the calculation of $t_{1/2}$ and the AUC parameters with the [redacted] software package differs from the approach described above (Section 10.1) for the summary of plasma concentrations. For the calculation of these parameters, BLQ values will be set equal to zero with the exception of BLQ values bounded by quantifiable values. BLQ values between quantifiable concentrations will be ignored (i.e., treated as missing values) for the calculation of these parameters.

11. SAFETY

Results will be presented using the safety analysis set, as described in Section 6.2.1.1.

11.1. Adverse Events

Adverse events are recorded in the electronic case report form (eCRF). Each AE will be coded to a SOC and PT using MedDRA (version 24.0).

A treatment-emergent adverse event (TEAE) is an adverse event not present prior to the initiation of study drug dosing or is an already present event that worsens either in intensity or frequency following the initiation of study drug dosing and also occurs on or before the last dose of study drug. Investigators will be asked to respond "Yes" or "No" on the CRF as to whether the AE started after the subject took the first dose of study drug. An AE with a response of "Yes", and that occurs on or before the last dose of study drug, will be classified as a TEAE. If the investigator's response is missing on the CRF, then the treatment emergent status will be derived based on the AE onset date and time relative to the date and time of the subject's first and last dose of study drug. If the AE onset date and time are unknown, it will be assumed that the AE is a TEAE. If the AE onset time is unknown but the AE onset date is the same date as the first dose of study drug, it will be assumed that the AE is a TEAE. Adverse events that occur after the last dose of study drug but on or before the last dose plus 21 days will be considered post-treatment emergent (post-TEAEs). Adverse events with an onset date after the last dose plus 21 days will not be considered treatment emergent (non-TEAEs).

TEAEs, post-TEAEs, and non-TEAEs categorized by MedDRA SOC and/or PT, will be summarized in frequency tables. The frequency tables will include the number and percentage of unique subjects experiencing each event one or more times.

Two similar frequency tables will be generated for TEAEs – one including both SOC and PT (each sorted in alphabetical order), and one including PT only, with PTs sorted in order of decreasing frequency of subjects reporting the PT. Post-TEAEs and non-TEAEs will be summarized by SOC and PT only (each in alphabetical order).

An overall summary table will be provided which summarizes the number and percentage of unique subjects with any TEAE, any TEAE leading to study discontinuation, any serious TEAE, and any TEAE resulting in death. The summary table will also include the frequency distribution of the maximum TEAE intensity (mild, moderate, severe). A subject with more than one event coded to the same PT will be classified according to the most severe event.

11.1.1. Adverse Events Resulting in Premature Discontinuation from Study

Summary tables of TEAEs resulting in early discontinuation from the study will be presented. The number and percentage of subjects with a TEAE resulting in study discontinuation will be presented by PT within SOC (presented in the same method as the analogous primary TEAE table). More than one AE can contribute to study discontinuation per subject. The first line of the table will display the number and percentage of subjects with at least one TEAE leading to study discontinuation.

A listing of TEAEs resulting in premature study discontinuation will be provided which includes subject ID, treatment, study day of the discontinuation, and other relevant information from the AE eCRF.

11.1.2. Deaths and Other Serious Adverse Events

Summary tables of serious adverse events (SAEs) will be presented. The number and percentage of subjects with an SAE will be presented by PT within SOC (each sorted in alphabetical order). The first line of the table will display the number and percentage of subjects with at least one SAE.

Separate listings of SAEs and fatal TEAEs will also be provided. Each listing will include subject ID, treatment group, study day of the SAE or fatal TEAE, and any additional relevant information from the AE eCRF.

11.2. Clinical Laboratory Data

The hematology, clinical chemistry, and [redacted] data will be summarized with descriptive statistics by visit. Both observed values and changes from baseline will be summarized.

A shift table from baseline to Day 15 will be presented for selected clinical laboratory variables based on the reference range-based categories of "Low," "Normal," or "High." A clinical laboratory variable value will be assigned to one of these three categories according to the reference ranges provided by the central clinical laboratory. The shift table will have three rows and three columns, with rows reflecting the reference range category at baseline, and columns reflecting the reference range category at Day 15. A "Total" row and "Total" column will also be included. Subjects with a missing baseline value or who do not have Day 15 data will not be included in the tables for that variable. The number and percentage of subjects in each shift category will be displayed in the table; percentages will be based on the number of subjects included in the table.

The shift table will be presented for the following clinical laboratory variables:

- aspartate aminotransferase (AST),
- alanine aminotransferase (ALT),
- alkaline phosphatase (ALP),
- gamma-glutamyl transferase (GGT),
- total bilirubin,
- creatine kinase,
- creatinine,
- blood urea nitrogen,
- white blood cell count,
- absolute neutrophil count,
- hemoglobin,

- platelet count,
- [redacted]
- [redacted]

Summaries of sponsor-defined potentially clinically significant (PCS) values will be presented for the following clinical laboratory variables: ALT, AST, creatine kinase, GGT, total bilirubin, white blood cell count, absolute neutrophil count, creatinine, and BUN. The number and percentage of subjects with PCS values that are reported at any postbaseline visit (scheduled or unscheduled) will be summarized. The criteria for identifying PCS clinical laboratory values are provided in Table 3.

Table 3: Potentially Clinically Significant Criteria for Clinical Laboratory Variables

Variable	PCS Threshold
ALT	>3 x ULN (upper limit of normal)
AST	>3 x ULN
Creatine kinase	>5 x ULN
GGT	>3 x ULN
Total bilirubin	>1.5 x ULN
White blood cell count	≤2.8 x 1000/µL
Absolute neutrophil count	<1.5 x 1000/µL
Creatinine	>1.5 x baseline value or > 1.5 x ULN
BUN	>30 mg/dL (> 10.71 mmol/L)

Repeat clinical laboratory samples may be collected at any time during this study due to either missing or abnormal results. The general rule for summarizing these data is to include the original sample results in summary tables. Exceptions to this rule are: (1) all available lab values will be used in the PCS tables and (2) if there are missing results from the original lab samples at screening, the results of a repeat screening sample will be substituted for the missing results in summary tables.

11.3. Vital Signs

The vital signs data, including orthostatic blood pressures and heart rate (calculated as standing value minus supine value), will be summarized with descriptive statistics by visit. Observed and change from baseline values will be summarized.

Summaries of sponsor-defined PCS values will be presented for systolic blood pressure, diastolic blood pressure, and heart rate. The number and percentage of subjects with PCS values that are reported at any postbaseline visit (scheduled or unscheduled) will be summarized. The criteria for identifying PCS vital signs values are provided in Table 4.

Table 4: Potentially Clinically Significant Criteria for Vital Signs Variables

Variable Name	PCS – Low if:			PCS – High if:		
	Observed Value is:	AND	Decrease from Baseline is:	Observed Value is:	AND	Increase from Baseline is:
Systolic Blood Pressure	<90 mmHg		≥20 mmHg	>180 mmHg		≥20 mmHg
Diastolic Blood Pressure	<50 mmHg		≥15 mmHg	>105 mmHg		≥15 mmHg
Heart Rate	<50 bpm		≥15 bpm	>120 bpm		≥15 bpm

Both supine and standing values of blood pressures and heart rate will be included in the identification and summary of PCS values.

11.4. Body Weight

The body weight data (in units of kilograms) will be summarized with descriptive statistics at baseline and each scheduled postbaseline visit. Both observed values and changes from baseline will be summarized.

11.5. Electrocardiogram

The triplicate ECG parameter values recorded at each timepoint for heart rate, PR interval, QRS duration, QT interval, and QTcF (corrected QT interval using Fridericia's formula) interval will be averaged (and rounded to the nearest whole number) for each subject and timepoint for the purpose of statistical summarization. Additionally, for the triplicate investigator overall categorical assessment (ie, Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant) at each timepoint, the outcome representing the greatest degree of abnormality will be selected for summarization.

Descriptive statistics for the observed values and changes from baseline will be presented for each of the ECG parameters by timepoint.

Frequency tables (number and percentage of subjects) will be presented for the overall categorical assessment at each timepoint.

Two additional categorical summaries (frequency tables displaying number and percentage of subjects) will be presented for the QTcF interval. For the first summary, the observed QTcF values at each timepoint will be classified as follows:

- Greater than 450 msec
- Greater than 480 msec
- Greater than 500 msec

For the second categorical summary, the changes from baseline to each subsequent timepoint will be classified as follows:

- Increase greater than 30 msec
- Increase greater than 60 msec

The same categorical summaries will be presented in frequency tables for values at any postdose timepoint (including unscheduled assessments) meeting the aforementioned criteria.

11.6. Columbia-Suicide Severity Rating Scale

The C-SSRS (Children's Version) data will be presented in the following summaries:

- Screening/lifetime assessment
- Screening/past 1 year assessment
- Baseline (Day 1) assessment
- Postbaseline assessments

Each summary will display the number and percentage of subjects who report "Yes" to specific C-SSRS items or categories of items (a category is assigned a "Yes" value if a "Yes" is reported for any item in the category). These C-SSRS items and categories are as follows:

- Suicidal Ideation Items

  (1) Wish to be dead
  (2) Non-specific active suicidal thoughts
  (3) Active suicidal ideation with any methods (not plan) without intent to act
  (4) Active suicidal ideation with some intent to act, without specific plan
  (5) Active suicidal ideation with specific plan and intent

- Suicidal Ideation Category: Any of items (1) through (5)
- Suicidal Behavior Items (not included for screening/past 1 year assessment)

  (6) Preparatory acts or behavior
  (7) Aborted attempt
  (8) Interrupted attempt
  (9) Non-fatal suicide attempt
  (10) Completed suicide (not reported for the screening/lifetime assessment)

- Suicidal Behavior Category: Any of items (6) through (10)
- Suicidal Ideation or Behavior Category: Any of items (1) through (10)

For the "all postbaseline assessments" summary, each subject's C-SSRS responses for all postbaseline assessments will be evaluated, and a "Yes" response for any assessment will be considered as a "Yes" for the subject.

In addition to the summaries described above, shift tables comparing postbaseline suicidal ideation scores to baseline scores will be presented. The shift table scores are defined as the following:

0 = No suicidal ideation
1 = Wish to be dead
2 = Non-specific active suicidal thoughts
3 = Active suicidal ideation with any methods (not plan) without intent to act
4 = Active suicidal ideation with some intent to act, without specific plan

5 = Active suicidal ideation with specific plan and intent

The shift tables will display the number and percentage of subjects within each cell of a 6 x 6 table for each treatment group, with the rows representing the baseline score and the columns representing the maximum score recorded across all postbaseline assessments (including both scheduled and unscheduled visits). Subjects missing either a baseline score or all postbaseline scores will not appear in the table.

11.7. Brief Psychiatric Rating Scale for Children

The Brief Psychiatric Rating Scale for Children (BPRS-C) includes 21 items and the severity of each item is rated on a 7-point scale (1=not present, 2=very mild, 3=mild, 4=moderate, 5=moderately severe, 6=severe, 7=extremely severe). The BPRS-C total score is calculated as the sum of the scores for the 21 items (total score range: 21 to 147). If any one of the 21 items is not scored (ie, has a missing value), the BPRS total score will be set equal to missing.

BPRS total score observed values and change from baseline values will be summarized with descriptive statistics by visit.

12. DEVIATIONS FROM PROTOCOL PLANNED ASSESSMENTS AND ANALYSIS

13. PERFORMANCE QUALIFICATION OF SAS® PROGRAMS

The analysis and summary of data from this study will be performed using SAS® 9.4 (or a later release if available). All SAS® programs used in the production of statistical analyses, tables, listings, and figures described in this SAP will undergo performance qualification (verification that the program produces the intended output) in accordance with department standard operating procedures. The performance qualification may include independent programming and/or peer review of the SAS® log files. In addition, tables, figures, listings, and statistical analysis output will be independently reviewed for completeness and accuracy.

14. REFERENCES

Auchus RJ, Arlt W. Approach to the patient: the adult with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2013 Jul;98(7):2645-55.

European Medicines Agency. Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials. March 2020.

United States Food and Drug Administration. Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency. Guidance for Industry, Investigators, and Institutional Review Boards. March 2020, updated January 2021.

15. APPENDIX

The following table provides the conversion factors for different types of glucocorticoids to hydrocortisone dose equivalents. This will be used to calculate the total daily glucocorticoid dose.

Table 5: Hydrocortisone Dose Equivalent Conversion

Glucocorticoid	Hydrocortisone dose equivalent conversion
Methylprednisolone	4×
Prednisolone	4×
Prednisone	4×
Dexamethasone	60×

Auchus and Arlt, 2013; Speiser et al., 2018.

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