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STATISTICAL ANALYSIS PLAN

Title:	An Open Label Evaluation of the Adrenal Suppression Potential and Trough Plasma Concentrations of Cortexolone 17α-Propionate (CB-03-01) Cream Applied Every 12 Hours for Two Weeks in Subjects 9 to <12 Years of Age with Acne Vulgaris
Protocol Number:	CB-03-01/28
Sponsor:	Cassiopea S.p.A. Via C. Colombo 1, 20020 Lainate (MI), Italy
[redacted] **Project Number:**	171-7151-208
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GLOSSARY OF TERMS

Abbreviation	Definition
AE	Adverse event
BMI	Body Mass Index
C_{12}	Trough plasma concentrations
CSR	Clinical Study Report
CST	Cosyntropin Stimulation Test
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
eCRF	Electronic Case report Form
EOS	End of Study
HPA	Hypothalamic-Pituitary-Adrenal
IGA	Investigator's Global Assessment
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PT	Preferred Term
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UPT	Urine pregnancy test
WOCBP	Woman of Childbearing Potential

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol 171-7151-208, "An Open Label Evaluation of the Adrenal Suppression Potential and Trough Plasma Concentrations of Cortexolone 17α-Propionate (CB-03-01) Cream Applied Every 12 Hours for Two Weeks in Subjects 9 to <12 Years of Age with Acne Vulgaris".

This SAP was created using clinical protocol 171-7151-208 dated February 18, 2016 with two administrative amendments (March 18 and May 19, 2016) and the Electronic Case Report Forms (eCRF) for protocol 171-7151-208 dated January 16, 2017 v2.0.

2 PURPOSE OF THE ANALYSES

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for protocol 171-7151-208. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The study objective is to determine: a) the adrenal suppression potential and b) the trough plasma concentrations associated with topical application of CB-03-01 cream, 1% in subjects with acne vulgaris.

3.2 Safety Endpoints

Safety endpoints include:

- Hypothalamic-Pituitary-Adrenal (HPA) Axis Response to Cosyntropin by Cosyntropin Stimulation Test (CST): Measurement of serum cortisol concentrations after stimulation of the adrenal cortex with cosyntropin at Screening, and Day 14 (or End of Study (EOS)). HPA axis suppression is defined as a post-stimulation serum cortisol level ≤18 µg/dL at Day 14 (or EOS).
- Trough Plasma Concentrations: Trough measurements of cortexolone 17α-propionate and cortexolone in plasma at Screening, Day 1, Day 7 and Day 14.
- Local and systemic Adverse Event (AEs).
- The severity of the following Local Skin Reaction (LSRs) [for face and trunk, separately]: telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning and pruritus at Day 1 (pre- and post-test article application), Day 7, and Day 14 (or EOS).
- Safety laboratory testing (hematology, clinical chemistry, and urinalysis) at Screening and Day 14 (or EOS).
- Physical examination/vital signs at Screening and Day 14 (or EOS).
- ECG at Screening and Day 14 (or EOS).
- UPTs (for all females of childbearing potential) at Screening, Day 1, and Day 14 (or EOS).

3.3 Other Endpoint

The overall severity of each subject's facial acne at Day 14 (EOS) will be assessed by the investigator or designee using the Investigator's Global Assessment (IGA) score.

4 STUDY DESIGN

This is an open-label, multicenter study in approximately 20 subjects 9 to <12 years of age with moderate to severe facial acne vulgaris (IGA score of 3 or 4) and obvious acne on the trunk (i.e., shoulders, upper chest, and/or back). The study will include a Screening Visit, a Baseline Visit (Day 1), and two (2) scheduled follow-up visits (Day 7 and Day 14). Subjects will apply 2 grams of the test article per application every 12 hours for 2 weeks.

The study schedule of events and assessment is presented in Table 1. Further details regarding the study may be found in the study protocol.

Table 1: Schedule of Events

PROCEDURES	Visit 1 Screening (Days -45 to -14)	Visit 2 Baseline Day 1	Visit 3 Day 7 ± 1	Visit 4 EOS[1] Day 14 ± 2
Informed Consent/Assent	X	X[2]		
Demographics	X			
Inclusion/Exclusion Criteria	X	Reconfirm eligibility		
Medical/Dermatological History	X			
Dermatologic Exam	X			
Physical Exam	X			X
Vital Signs, Height, and Weight[3]	X			X
UPT[4] (females of childbearing potential)	X	X		X
ECG	X			X
Safety Labs (Hematology, Chemistry and Urinalysis)[5]	X			X
Urine Drug Screen	X			
Virus Screen (HIV, HCV, HBV)	X			
Investigator's Global Assessment	Confirm eligibility	X		X
Lesion Counts	Confirm eligibility	X		
LSR Assessment		X (pre- & post-application)	X	X
PK Blood Draws[6]	X	X	X	X
Cosyntropin Stimulation Test (CST)[7]	X	Confirm eligibility		X
Study Medication Dispensed & Collected[8]		X	X	X
Study Treatment (q. 12 hours)		X	X[9]	
Percent BSA to be treated		X		
Weigh Test Article/Verify Compliance		X	X	X
AEs Evaluation	X	X	X	X
Review of Concomitant Medications & Procedures	X	X	X	X

[1] Subjects who terminate early shall complete all final visit activities designated at Day 14 with the exception of the PK blood draws.
[2] Subjects who were consented for longer than 45 days prior to the Baseline Visit will be re-consented prior to enrolling into the treatment phase of the trial.
[3] Height and weight at Visit 1 only.
[4] Testing will be conducted on all females of childbearing potential. UPT minimal sensitivity is 25 mIU/mL.
[5] Laboratory test results will indicate if the subject was fasting. Screening laboratory tests will be conducted with the subject fasting and EOS laboratory tests are preferred to be in a fasting state.
[6] PK blood draws at Visit 3 and Visit 4 will occur 12 hours (± 30 minutes) after the evening application on the prior day.
[7] CST will be performed at Visits 1 and 4 as indicated. If results at the Day 14 visit show an abnormal CST response, testing will be performed at 4-week intervals until CST response has been documented to return to normal.
[8] Instruct subject on test article application and provide instruction sheet.
[9] Withhold morning application until after trough PK blood draw.

5 DEFINITIONS

- End of Study (EOS): Visit 4 or Early Termination Visit
- Completed Subject: A subject is considered to have completed the study if the subject completed the study treatment.
- Study Day: They study day is the day of study relative to the first dose (Baseline visit/Day 1) of the test article.
  Study Day = follow-up visit date – first dose date + 1
- Baseline in Change from Baseline: The baseline assessment in change from baseline is defined as the last non-missing measurement collected at Screening or Day 1 visit prior to the test article application.
- Treatment Area: The area defined by the investigator to which the test article is applied and which includes the face and trunk.

6 CLINICAL EVALUATIONS

6.1 Investigator's Global Assessment

IGA will be performed at Screening, Day 1 and Day 14 (EOS). Overall severity of acne on the face will be assessed using a 5-point scale from 0=clear to 4=severe by the investigator. This is a static morphological scale that refers to a point in time and not a comparison to Baseline. Subjects must have an IGA score of 3 (moderate) or 4 (severe) on the face at the Screening Visit.

Investigator's Global Assessment (IGA)		
Score	**Definition**	**Guideline**
0	Clear	Absence of active disease with no inflammatory or non-inflammatory lesions.
1	Almost Clear	Rare non-inflammatory lesions with no more than one small inflammatory lesion.
2	Mild	Some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only; no nodular/cystic lesions).
3	Moderate	Up to many non-inflammatory lesions and may have some inflammatory lesions but no more than one nodular/cystic lesion.
4	Severe	Up to many non-inflammatory lesions and inflammatory lesions but no more than a few nodular/cystic lesions.

6.2 Acne Lesion Counts

The number of inflammatory lesions (papules, pustules, and nodules/cysts) and non-inflammatory lesions (open and closed comedones) on the face will be counted separately at the Screening and Day 1 visits. Subjects must have at least 15 inflammatory lesions and at least 15 non-inflammatory lesions on the face at the Screening.

6.3 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, without any judgment about causality. A treatment emergent AE (TEAE) is defined as an AE that started on or after the first dose date.

The severity of an AE will be recorded as mild, moderate or severe. The relationship between an AE and the test article will be classified as definitely related, probably related, possibly related, unlikely related or not related. The AE action taken with study treatment will be specified as dose not changed, dose increased/reduced, drug interrupted/withdrawn, unknown, and not applicable. The other action taken will be collected as none, concomitant medication, lab test, concurrent procedure, non-drug therapy, or other. The outcome of the AE will be categorized as fatal, not recovered/not resolved, recovered/ resolved with sequelae, recovered/resolved, recovering/resolving or unknown.

A Dose Limiting Toxicity (DLT) is defined as a systemic Grade 2 or higher (CTCAE, Version 4.0) AE for which there is no clear alternative explanation of the cause of the AE. Non-systemic (local) AEs Grade 3 or higher for which there is no clear alternative explanation of the cause of the AE will also be considered DLTs.

6.4 Local Skin Reactions

LSRs will be collected separately for the face and trunk at Days 1 (before and after first application), 7, and 14 (EOS).

The investigator or designee will assess the LSRs using the five-point or four-point ordinal scales as follows:

LSRs	Scales
Telangiectasia, Skin atrophy, Striae rubrae	0 = none, 1= trace, 2 = mild, 3 = moderate, and 4 = severe
Erythema, Edema, and Scaling/dryness	0 = none, 1= minimal, 2 = mild, 3 = moderate, and 4 = severe
Stinging/burning	0 = none, 1= minimal, 2 = moderate, and 3 = severe
Pruritus	0 = none, 1= mild, 2 = moderate, and 3 = severe

Further details regarding the description of the scales can be found in the study protocol.

6.5 Cosyntropin Stimulation Test

CST will be performed at Screening and Day 14 (or EOS). If a subject's laboratory results at Day 14 (or EOS) show an abnormal HPA axis response (defined as a post-stimulation serum cortisol level of ≤18 μg/dL), the test article will be considered to have caused the abnormal CST result in the subject and the subject should return for follow-up visits until the HPA axis response has been documented to return to normal.

6.6 Blood Draw for Morning Trough Concentrations

Blood samples will be collected for morning trough concentrations (C_{12}) of cortexolone 17α-propionate and cortexolone in plasma at Screening, Day 1 (pre-dose), Day 7 and Day 14.

6.7 Physical Examination, Vital Signs, ECGs and Safety Laboratory Tests

Findings from the physical examinations will be recorded in medical history (from assessment at Screening) or as AEs (from assessment at Day 14 (EOS)).

Vital Signs, ECGs, and safety laboratory data are to be collected at Screening and Day 14 (or EOS). Urine pregnancy test (UPT) for women of childbearing potential (WOCBP) will be performed at Screening, Days 1 and 14.

6.8 Concomitant Medications and Concurrent Therapies/Procedures

Details of prior and concomitant medication use and concurrent therapies/procedures will be collected throughout the study.

7 STATISTICAL METHODS

7.1 General Considerations

This section presents the statistical approaches that are anticipated for the analysis of the study data. These approaches may at times require modifications due to unanticipated features of the data. Deviations from analyses summarized in this document will be noted in the CSR.

Version 9.4 (or higher) of the SAS statistical software package will be used to provide summary tables and data listings, unless otherwise stated.

For continuous variables, descriptive statistics will include the number of subjects with non-missing data (n), mean, median, standard deviation, minimum and maximum values. For categorical variables, the number and percentage of subjects within each category will be presented. Subject data listings sorted by study site and subject number will be presented. Summaries and analyses will be provided as specified below.

7.2 Analysis Populations

All subjects will be classified into the Safety, Evaluable, and Pharmacokinetic (PK) populations according to the following definitions.

7.2.1 *Safety Population*

The Safety population will include all enrolled subjects who were dispensed and applied at least one dose of the test article.

7.2.2 *Evaluable Population*

The evaluable population will include those subjects in the safety population who have both Screening and Day 14 serum cortisol data (pre- and post-cosyntropin stimulation) and meet the following criteria:-

- Meets all inclusion/exclusion criteria, including normal response to cosyntropin stimulation defined as a Screening CST with a 30-minute post-stimulation cortisol level of > 18 μg/dL.
- Screening and Day 14 CST were conducted between 7-9 AM.
- Day 14 CST was conducted within ±1 hour of the Screening CST.
- Applied at least 80% of expected applications and applied the final dose no more than 14 hours prior to the start of the CST test.
- Has not taken or applied any medications that may interfere with HPA axis function.
- Do not have any other significant protocol deviations.

HPA axis suppression analysis will be conducted on the Evaluable population.

7.2.3 *Pharmacokinetic Population*

The PK population will include those subjects in the Safety population who have at least an 80% dose compliance based on number of applications, have at least one post-baseline PK blood draw within ±2 days of the scheduled visit at Days 7 and 14, and do not have any significant protocol deviations. For subjects who are in the PK population but did not apply the final three doses prior to the PK blood draw at Day 14, their Day 14 data will be excluded. For subjects in the PK population who discontinued from the study prematurely, their Screening, Day 1 and Day 7 data will be included as long as their dose compliance up to Day 7 is at least 80%.

The morning trough concentrations of cortexolone 17α-propionate and cortexolone will be presented for the PK population.

7.3 Final Analyses and Reporting

Final database lock will occur after all subjects have completed the study assessment period (or discontinued early) and all subject data has been monitored. Analysis may not occur until after database lock, this SAP is approved, and analysis populations have been identified.

7.4 Methods for Handling Missing Data

All summaries and analyses will use observed data only.

7.5 Sample Size

No formal sample size calculations were performed. The number of evaluable subjects (20) is historically consistent with other HPA/PK studies.

7.6 Subject Disposition

The number and percentage of subjects who were enrolled in the study, who completed the study, who withdrew from the study and their reasons for discontinuation will be tabulated for each analysis population.

Subject data listings of the protocol deviations, if any, and analysis population identification will be provided.

7.7 Screening and Baseline Assessments

7.7.1 *Demographics*

Demographic information including age, sex, ethnicity, race will be summarized for each analysis population. The demographic data for screen failures will be listed separately.

7.7.2 *Medical History, Dermatological Examination and Physical Examination*

Medical history, dermatological examination, and abnormalities noted during the physical examination at Screening will be presented in subject data listings for the Safety population.

7.7.3 *Baseline Vital Signs, Height and Weight*

Descriptive statistics will be provided for Baseline vital signs (blood pressure, pulse rate, temperature, and respiration rate), height, weight and BMI for the Safety population.

7.7.4 *Baseline Clinical Evaluations*

Baseline IGA and inflammatory and non-inflammatory lesion counts will be summarized for the Safety population.

Baseline LSRs will be tabulated for the Safety population.

7.7.5 *Extent of Exposure*

The total amount of test article used by each subject (difference between the weight of the tubes dispensed and weight of the tubes returned) and the mean daily amount of test article applied (total amount of test article used divided by the treatment duration) will be calculated. The treatment duration is calculated by last dose date - first dose date +1. Descriptive statistics will be used to summarize the total amount and mean daily amount of test article applied for each analysis population.

7.7.6 *Dosing Compliance*

Dosing compliance (%) is derived by the following formula:

$$\frac{\text{Total number of applications}}{\text{expected applications}} \text{ x } 100,$$

where expected applications are 26 considering 13-day course of planned treatment for subjects who completed the study; and (study day of the last dose)x2 for subjects who discontinued from the study prematurely.

Descriptive statistics will be used to summarize test article dosing compliance. Subjects who applied at least 80% of the expected applications will be considered to be compliant with test article dosing.

7.8 Safety Analyses

Summaries of the safety parameters will be provided as described below for the Safety population, unless otherwise specified.

7.8.1 *Adverse Events*

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. Verbatim terms will be mapped into a MedDRA system organ class (SOC) and preferred term (PT). For all AE summaries, if a subject has more than one AE within a PT, the subject is counted once in that PT. If a subject has more than one AE within a SOC, the subject is similarly counted once in that SOC.

The number and percentage of unique subjects reporting any local and systemic treatment-emergent AE will be summarized by SOC and PT. The number and percent of unique subjects reporting any local and systemic TEAE will also be summarized by SOC, PT, and maximum severity (mild, moderate, severe) and closest relationship to test article (not related, unlikely, possibly, probably related).

Serious AEs and DLTs, if any, will be listed separately.

7.8.2 *HPA Axis Suppression Analysis*

HPA axis responses to cosyntropin will be dichotomized to normal and abnormal. An abnormal HPA axis response (HPA suppression) is defined as a 30-minute post-stimulation serum cortisol level of ≤18 μg/dL at Day 14. The proportion of subjects manifesting laboratory based evidence of adrenal suppression at Day 14 will be presented along with 95% confidence intervals for the Evaluable population. The observed serum cortisol levels (pre- and post-cosyntropin stimulation) and the changes in serum cortisol levels after stimulation at Screening, Day 14, and, if any, at follow-up visits will also be summarized.

7.8.3 *Trough Concentrations*

Morning trough concentrations (C_{12}) of cortexolone 17α-propionate and cortexolone in plasma at Screening, Day 1, Day 7 and Day 14 will be summarized for the PK population using geometric mean, coefficient of variation in addition to n, mean, median, standard deviation, minimum and maximum.

Individual trough concentrations of cortexolone 17α-propionate and cortexolone in plasma across visits will be plotted. Individual average trough concentrations of cortexolone 17α-propionate and cortexolone will also be plotted by adrenal suppression status.

7.8.4 *Local Skin Reactions*

Severity of LSRs (telangiectasia, skin atrophy, striae rubrae, erythema, edema, and scaling/dryness, stinging/burning, and pruritus) will be tabulated by frequency and severity

of each individual LSR at each visit. The counts of worsened and same/improved based on the change from baseline score will be also presented.

7.8.5 *Vital Signs and Electrocardiograms*

Descriptive statistics will be used to summarize vital signs and ECG at Screening and Day 14 (EOS) and change from baseline in vital signs at Day 14 (EOS). Clinically significant findings will be additionally listed.

7.8.6 *Safety Laboratory Tests*

Safety laboratory data (hematology, clinical chemistry, and urinalysis) will be tabulated at Screening and Day 14 (EOS) and Change from Baseline at Day 14 (EOS) will also be summarized. All laboratory data will be listed and reported in the units received by the central laboratory. Shift tables by analyte and by out of reference range flag (Normal, Low, and High) will be presented to facilitate the evaluation of change from Baseline to Day 14 (EOS).

7.8.7 *Urine Pregnancy Tests*

Results of the UPT at Screening, Day 1 and Day 14 (EOS) will be provided in a subject data listing.

7.8.8 *Concomitant Medications and Concurrent Therapies/Procedures*

Concomitant medications will be coded using the WHO Drug dictionary version September 1, 2016. Concomitant medications and concurrent therapies/procedures will be presented in subject data listings.

7.9 Other Analysis: Investigator's Global Assessment

The frequency distributions of IGA score will be tabulated at Baseline and Day 14 (EOS) for the Safety and the Evaluable populations.

7.10 Subgroup Analyses

No subgroup analyses are planned.

7.11 Interim Analysis and Study Stopping Rule

No interim analyses are planned. If more than three subjects experience DLTs in the study, enrollment in the trial will be stopped.

8 Planned Listings, Tables and Figures

All tables and listings will be presented in landscape orientation.

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