STATISTICAL ANALYSIS PLAN

CRO study code CRO-MT-15-014 - Sponsor code CB-03-01/27

AN OPEN-LABEL, LONG-TERM EXTENSION STUDY TO EVALUATE THE SAFETY OF CORTEXOLONE 17α-PROPIONATE (CB-03-01) CREAM, 1% APPLIED TWICE DAILY IN SUBJECTS WITH ACNE VULGARIS

Multicenter, open-label, long-term extension study

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Test product: CB-03-01 cream containing 1% cortexolone 17α-propionate (BID)

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This study was conducted in accordance with Good Clinical Practice (GCP), ICH topic E6

This document comprises 23 pages plus appendices

STATISTICAL ANALYSIS PLAN APPROVAL

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Statistical Analysis

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STUDY SCHEDULE

Visit	Visits 1-4 Pivotal Phase 3	Visit 4- LTF Baseline	Visit 5	Visit 6	Visit 7 Phone Call 1	Visit 8	Visit 9 Phone Call 2	Visit 10[1] EOS	Unscheduled
Long-Term Follow-Up (LTF): Month Day		**0 1[2]**	**1 29 ± 10**	**3 85 ± 15**	**4.5 137 ± 15**	**6 183 ± 15**	**7.5 228 ± 15**	**9 274 ± 21**	**If/As Needed**
Overall CB-03-01 Exposure: Month[3]	**0 or 3**	**0 or 3**	**1 or 4**	**3 or 6**	**4.5 or 7.5**	**6 or 9**	**7.5 or 10.5**	**9 or 12**	
PROCEDURES	**See Phase 3**								
Informed Consent/Assent[4]		X[4]							
Inclusion/Exclusion Criteria		X							
Demographics		From Phase 3[5]							
Medical/Dermatological History		From Phase 3[5]							
Physical Exam with Vital Signs		X							
UPT for WOCBP		X[6]				X		X	
IGA (Face and Trunk, separately)		Face: From Phase 3[7] Trunk: X[8]	X	X		X		X	X
Determination of Test Article Dosing		X	X	X		X		X	X
LSRs Assessment (Face and Trunk, separately)		X[9]	X	X		X		X	X
AEs		X	X	X	X	X	X	X	X
Concomitant Medications & Procedures		From Phase 3[10]	X	X	X	X	X	X	X
Dispense & Collect ITA[11,12]		X	X	X		X		X	X
Review of Compliance			X	X	X	X	X		X

1 Subjects who terminate early shall complete all final visit activities.
2 For this LTF study, subjects must rollover from the Phase 3 pivotal study (CB-03-01/25 and CB-03-01/26) into this study AT or WITHIN THREE (3) DAYS of Visit 4-Pivotal.
3 Given that the Phase 3 pivotal trial is randomized (1:1) between active (CB-03-01 cream, 1%) and vehicle, upon entering the LTF study, some subjects had an overall exposure to CB-03-01 cream, 1% of 3 months and others had 0 months (i.e., subjects were treated with vehicle in the Pivotal study).
4 Consent/assent may be performed up to 45 days prior to the Baseline Visit.
5 Demographics and medical/dermatological history were used from the Phase 3 pivotal study (Visit 1-Pivotal).
6 If Visit 4-Pivotal and Visit 4-LTF occur on the same day, the results of the UPT performed during the End of Study (EOS) visit of the Phase 3 pivotal study can be used as Baseline data.
7 IGA performed at the EOS Visit of the Phase 3 pivotal trial were used as Baseline data (Visit 4-Pivotal).
8 If truncal acne is to be treated (as designated by the investigator AND desired by subject), identify the percent body surface area (BSA) to be treated. BSA was estimated based on the assumption that 1% BSA is equivalent to the area of the subject's hand with fingers held together.
9 LSRs assessed at the EOS Visit of the Phase 3 pivotal trial (Visit 4-Pivotal) were used as pre-application data for face. LSRs [pre-application] were assessed for trunk at Visit 4-LTF. After ITA application in the clinic, LSRs were assessed post-application (Visit 4-LTF) for face and trunk, as applicable.
10 Any ongoing concomitant medications and procedures were reviewed at Visit 4-LTF.
11 Instruct subject (and parent/guardian, if applicable) on ITA application and provide instruction sheet. Review compliance with respect to the amount and number of doses applied since the last visit.
12 Dispense subject diary, as needed.

LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification system
BID	Twice a day
BSA	Body Surface Area
CB-03-01	Cortexolone 17α-propionate
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
CV%	Percent Coefficient of Variation
EDC	Electronic Data Capture
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HPA	Hypothalamic-Pituitary-Adrenal
ICH	International Conference of Harmonization
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITA	Investigational Test Article
ITT	Intent-to-Treat
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
LSR	Local Skin Reaction
LTF	Long-Term Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-Counter
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UPT	Urine Pregnancy Test
WOCBP	Women of Childbearing Potential

1. INTRODUCTION

Statistical analysis will be performed by the [redacted]. The present Statistical Analysis Plan (SAP) specifies the analyses of the data from clinical study protocol CB-03-01/27. The endpoints and methods of analysis specified in this SAP are consistent with ICH E9 guidelines (1), with the FDA draft guidance for industry on Ance Vulgaris (2) and with the study protocol (3). The SAP has been compiled by the [redacted] reviewed by the Sponsor and finalized before the EDC database lock.

1.1 Changes with respect to the study protocol

No change with respect to the study protocol.

2. STUDY DESCRIPTION

2.1 Background

CB-03-01 (cortexolone 17α-propionate) is a steroidal antiandrogen that is being developed as a 1% cream for the topical treatment of acne vulgaris, an androgen-dependent skin disorder. CB-03-01 binds to the human androgen receptor displacing the androgenic hormones and acts as an androgen antagonist. In human plasma, CB-03-01 is rapidly metabolized to parent cortexolone so that its systemic bioavailability after topical application is anticipated to be low. Cortexolone, the main by-product, is a physiological component of the pool of endogenous corticosteroids, and is an intermediate in the synthesis of glucocorticoids, but it only exhibits weak glucocorticoid properties (4).

CB-03-01 could offer advantages over existing products for acne vulgaris due to its potential efficacy and lack of systemic antiandrogen activity. Because its pharmacological action appears to be limited to the local site of application, use of CB-03-01 may be able to mitigate the side effects related to systemic exposure to hormonal agents currently used in the treatment of acne.

2.2 Rationale

To date, CB-03-01 cream has been used for treatment of acne vulgaris for up to 12 weeks with no material safety issues to note. Given that acne vulgaris is a chronic condition which typically waxes and wanes over time and often requires extended (and sometimes intermittent) treatment, this study is designed to investigate the long-term safety of CB-03-01 cream, 1%.

2.3 Study Objectives

The primary objective of this study is to determine the long-term safety of CB-03-01 cream, 1% applied twice daily for an additional nine months in subjects with acne vulgaris that participated in the Phase 3 pivotal studies for a total treatment of up to 12 months.

2.4 Study Design

This is a multicenter, open label, long-term extension study for CB-03-01 cream, 1% focused on safety in male and female subjects, 9 years or older who completed one of the Phase 3 pivotal studies [CB-03-01/25 and CB-03-01/26]. Subjects applied the active medication (CB-03-01 cream, 1%) twice daily to the entire face and, if designated by investigator AND desired by subject, truncal acne for nine additional months of treatment. Thus, overall subjects were exposed to CB-03-01 cream, 1% for a total treatment of up to 12 months (0 or 3 months in the Phase 3 pivotal study and an additional nine months in this long-term safety study).

For this Long-Term Follow-Up (LTF) study, subjects must rollover from the Phase 3 pivotal study (CB-03-01/25 and CB-03-01/26) into this study AT or WITHIN THREE (3) DAYS of Visit 4-Pivotal.

Refer to section 4 of the study protocol (3) for further details.

2.5 Study Population

Male and female subjects 9 years or older with facial acne vulgaris who were enrolled in one of the Phase 3 pivotal studies (CB-03-01/25 and CB-03-01/26), completed the assigned treatment regimen without any material non-compliance with study requirements or test article dosing (compliance ≥ 80%) and completed the final study visit.

609 subjects were included into the study and 75 sites participated in this study.

2.5.1 Subject Eligibility

To be included in the study, subjects had to meet the inclusion criteria and none of the exclusion criteria reported in the section 5.1.1 and 5.1.2 of the study protocol (3).

2.5.2 Subject Withdrawal Criteria

Procedures for handling subjects who were discontinued from the study are described in section 13.2 of the study protocol (3).

2.6 Randomization Assignment

There is no randomization assignment in this study. This is an open label, extension study in which all eligible subjects are treated with CB-03-01 cream, 1% (i.e., the test article). 609 subjects were enrolled in this extension study in order to achieve at least 300 subjects on-study at 6 months and 100 subjects on-study at 12 months. These treatment durations include the 0 or 3 months of active treatment in the Phase 3 pivotal studies (CB-03-01/25 and CB-03-01/26). Enrollment was competitive; upon enrollment of 600 subjects in this study, the option for rollover was not offered to other subjects in the Phase 3 pivotal studies (CB-03-01/25 and CB-03-01/26), even if those subjects were eligible. Enrolled subjects were provided with labeled test article during the study period, as needed. Subject numbers were carried over from the Phase 3 pivotal study (CB-03-01/25 or CB-03-01/26).

3. CLINICAL EVALUATIONS

The following clinical evaluations were performed according to the schedules indicated during the study. The same investigator should complete the evaluations for a given subject throughout the study. If this becomes impossible a sub-investigator with overlapping experience with the subject and the study should complete the evaluations.

3.1 Investigator's Global Assessment (IGA)

Overall severity of acne using a five-point scale from 0=clear to 4=severe was evaluated for the face and trunk, separately. This is a static morphological scale that refers to a point in time and not a comparison to Baseline. IGA performed on the face during the End of Study (EOS) Visit of the Phase 3 pivotal study (i.e., Visit 4-Pivotal) and IGA performed on the trunk at Visit 4-LTF were used as Baseline data.

Score	Assessment	Description
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 lesions
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

IGA, to document acne improvement (i.e., achieves an IGA of grade 0 or "minimal" grade 1) or worsening (IGA $\geq$ 2), was also assessed to support treatment recommendations at regularly scheduled visits and any unscheduled visits, as needed.

3.2 Local Skin Reactions (LSRs)

At every in-clinic study visit and unscheduled visits, the investigator or designee documented the severity of the following LSRs known to be associated with application of topical steroids in the treatment areas (face and trunk, separately):

1. Telangiectasia
2. Skin atrophy
3. Striae rubrae

A five-point ordinal scale was used to assess the severity of these reactions:

Score	Assessment
0	None
1	Trace

Score	Assessment
2	Mild
3	Moderate
4	Severe

In addition, the investigator or designee evaluated the severity of the following LSRs known to be associated with acne vulgaris in the treatment areas (face and trunk, separately), using the five-point ordinal scales described below:

4. Erythema
5. Edema
6. Scaling/dryness

Erythema Score	Assessment
0	None
1	Minimal - barely perceptible erythema
2	Mild - predominantly minimal erythema (pink) in the treated area with or without a few isolated areas of more intense erythema
3	Moderate - predominantly moderate erythema (red) in the treated area with or without a few isolated areas of intense erythema (bright red)
4	Severe - predominantly intense erythema (bright red) in the treated area with or without a few isolated areas of very intense (fiery red) erythema

Edema Score	Assessment
0	None
1	Minimal - scant, rare edema
2	Mild - easily seen edema, minimally palpable, involving up to 1/3 of the Treatment Area
3	Moderate - easily seen edema and typically palpable, involving between 1/3 to 2/3 of the Treatment Area
4	Severe - easily seen edema, indurated in some areas, involving over 2/3 of the Treatment Area

Scaling/dryness Score	Assessment
0	None
1	Minimal - barely perceptible desquamation
2	Mild - limited areas of fine desquamation in up to 1/3 of the treatment area
3	Moderate - fine desquamation involving 1/3 to 2/3 of the treatment area or limited areas of coarser scaling

Scaling/dryness Score	Assessment
4	Severe - coarser scaling involving more than 2/3 of the treatment area or limited areas of very coarse scaling

In addition, subjects were asked to rate the severity of the following LSRs that occurred in the treatment areas (face and trunk, separately) since the last visit, using the four-point ordinal scales described below:

7. Stinging/burning
8. Pruritus

Stinging/burning Score	Assessment
0	None
1	Minimal, barely perceptible - tolerable and little discomfort
2	Moderate - tolerable, but causes some discomfort
3	Severe - very uncomfortable or intolerable

Pruritus (itching) Score	Assessment
0	None - no evidence of itching
1	Mild - only aware of itching at times, only present when relaxing, not present when focused on other activities
2	Moderate - often aware of itching, annoying, sometimes disturbs sleep and daytime activities
3	Severe - constant itching, distressing; frequent sleep disturbance, interferes with activities

These LSRs were collected independently of AEs. Only LSRs that require medical intervention (e.g., prescription medication) or require withholding the application of the test articles will be documented as AEs. Any LSRs that are not listed above will be recorded as AEs.

3.3 Truncal Body Surface Area (BSA)

Treatment of truncal acne was discussed by the investigator and subject. If the subject desired, the truncal treatment area was defined and agreed upon by the investigator and the subject with the percent BSA to be treated recorded. Percent BSA to be treated was estimated using the assumption that 1% BSA is equivalent to the area of the subject's hand with fingers held together. Once this truncal treatment area had been defined, the subject had to continue to treat this area for the remainder of the study until the area was clear (an IGA of grade 0 or "minimal" grade 1) as determined by the investigator and then re-initiate treatment (as/if required) per protocol for worsening. See section 6.2 of the study protocol (3) for further details.

4. PHOTOGRAPHY

Photography documentation was not required in this study. However, the investigator might elect to photograph the subject to document the effects of treatment, AEs or other findings during the trial. All photographs taken as part of this study are for informational purposes only and are not to assist in grading or for any other assessment.

5. LABORATORY TESTS

5.1 Urine Pregnancy Tests (UPTs)

The UPT was performed at the study site if the site met local country requirements to perform the testing (e.g., United States sites registered and conforms to Clinical Laboratory Improvement Amendments (CLIA) regulations for such testing [site possesses at a minimum a current valid CLIA Certificate of Waiver]) or at an appropriately registered reference laboratory. A UPT was performed at Visit 4-LTF (or Visit 4-Pivotal, if the visits occur on the same day) (i.e., Baseline), Visit 8 (LTF-Month 6), and Visit 10 (EOS) on all WOCBP (see Section 5.1 for definition). The investigator reported the UPT results on the CRFs, in the subject's medical records and, if applicable, in independent records maintained at the study site. The UPT used had to have a minimum sensitivity of 25 mIU of β-HCG/mL of urine.

6. STATISTICAL CONSIDERATIONS

6.1 Study Endpoints

6.1.1 Safety Endpoints

Safety endpoints will include:

- Incidence of any local and systemic treatment emergent AEs (TEAEs).
- Number of subjects with presence (and severity) of each individual LSR (telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus) for each treatment area, as applicable, at each time point collected (Baseline, and LTF-Months 1, 3, 6 and 9, and any Unscheduled Visits).
- UPT results in all WOCBP at Baseline, LTF-Month 6 and EOS.

6.1.2 Efficacy Endpoints

Efficacy Endpoints will include:

- Number of subjects with each IGA severity score for each treatment area, as applicable, at each time point collected (Baseline and LTF-Months 1, 3, 6 and 9).

6.2 Hypothesis Tests

No formal hypothesis test will be performed.

6.3 Sample Size Calculations

For large samples, the two-sided confidence interval for a single proportion extends a distance

$$\omega = z_{1-\frac{\alpha}{2}}\sqrt{\frac{\pi(1-\pi)}{n}}$$

from the observed proportion in both directions.

An incidence no greater than 1% of important AEs out of 100 subjects will provide the estimate of no greater than a 3% prevalence of important AEs at the 95% confidence level with a much larger number of subjects exposed for the same duration (i.e., 12 months). Applying the same approach, an incidence no greater than 1% of important AEs out of 300 subjects will provide the estimate of no greater than a 2.1% prevalence of important AEs at the 95% confidence level with a much larger number of subjects exposed for the same duration (i.e., 6 months).

Approximately six hundred (600) subjects had to be enrolled in order to have 300 subjects on-study at 6 months and 100 subjects on-study at 12 months. These treatment durations include the 0 or 3 months of active treatment in the Phase 3 pivotal studies (CB-03-01/25 and CB-03-01/26).

7. STATISTICAL METHODS

All statistical processing will be performed using SAS for Windows Version 9.3 (TS1M1) (5) (or higher) unless otherwise stated. Summary tables (descriptive statistics and/or frequency tables) will be provided for baseline variables, efficacy variables and safety variables. Continuous variables will be described by descriptive statistics (n, mean, standard deviation, CV%, minimum, median and maximum). Frequency counts and percentage of subjects within each category are provided for categorical data.

7.1 Tables, Listings and Figures layout

Tables and Listings will be provided according to the following settings:

- Background: White
- Foreground: Black
- Font face: Times
- Font style: Roman
- Font size: 10 pt
- Font weight: Medium (data, footers and notes), Bold (titles and headers)
- Font width: Normal
- Layout: Landscape
- Top Margin: 0.8 cm
- Bottom Margin: 0.8 cm
- Left Margin: 0.8 cm
- Right Margin: 0.8 cm
- Test label: CB-03-01
- Date format: ddMMMyyyy
- Means, standard deviations, percent coefficient of variations, medians, lower confidence limits and upper confidence limits will be rounded to one digit more than the original data
- Minima and maxima will keep the same number of decimal digits as the source values

7.2 Analysis sets

Subjects who completed 6 months or 12 months on-study without material non-compliance with test article (CB-03-01 cream, 1%) dosing per protocol will count towards the desired 300 subjects at 6 months and 100 subjects at 12 months.

The following analysis sets will be defined:

1. Intent-to-Treat Set (ITT): all enrolled subjects. This analysis set will be used for efficacy analyses.

2. Per Protocol Set (PP): all enrolled subjects who completed the study without any significant protocol deviations. This analysis set will be used for efficacy analyses.

3. Safety Set: all subjects who received at least one application of the test article. This analysis set will be used for safety analyses.

7.2.1 Exclusion from the Per Protocol Set

Reasons for the exclusion from the Per Protocol Set include the following:

1. failure to satisfy any inclusion/exclusion criteria (eligibility violations);
2. intake of prohibited medications.

The precise reasons for excluding subjects from the per protocol set will be fully defined and documented in the data review meeting/conference report.

7.3 Evaluation of Treatment Compliance

Compliance to the test article will be evaluated at each visit and overall according to the following formula:

$$\textbf{Compliance} = 100 \times \frac{\textbf{Number of actual applications}}{\textbf{Number of scheduled applications}}$$

Non-compliance will be defined as a compliance value less than 80%.

7.4 Handling of missing data

Missing data will not be replaced.

7.5 Demographic, baseline and background characteristics and other study information

Demographic, baseline and background characteristics will be reported for all the enrolled subjects and analyses will be performed according to the treatment the subjects actually received.

7.5.1 Subjects' disposition

The disposition of all subjects enrolled in the study will be listed and summarised. The number and percentage of subjects completing the study, the number and percentage of withdrawals and the reasons for withdrawal will be presented (Listing 16.2.4.1, Table 14.1.1.1).

7.5.2 Analysis sets

The subjects included in each analysis sets will be listed and summarised (Listing 16.2.4.2, Table 14.1.1.2).

7.5.3 Subjects on-study

The number and percentage of subjects who were on-study at 3, 6, 9 and 12 months will be presented (Table 14.1.1.3, Table 14.1.1.4, Table 14.1.1.5).

7.5.4 Subjects excluded from efficacy and/or safety analysis

All subjects excluded from the efficacy and/or safety analysis will be listed and the reasons for exclusion will be reported (Listing 16.2.3.1).

7.5.5 Discontinued subjects

All subjects who discontinued the clinical trial will be listed. Sex, age, last visit performed before discontinuation, type of discontinuation, date of premature discontinuation and primary reason for subject premature discontinuation will be reported (Listing 16.2.1.1).

7.5.6 Demography

Demographic data will be listed and summarised. The number and percentage of subjects in each category of categorical variables (e.g. sex) and the descriptive statistics (mean, standard deviation, CV%, minimum, median and maximum) of continous variables (e.g. age) will be presented (Listing 16.2.4.3, Table 14.1.1.6, Table 14.1.1.7, Table 14.1.1.8).

7.5.7 Inclusion/Exclusion criteria

All the unmet inclusion/exclusion criteria will be listed and summarised. The number and percentage of subjects for each skin type will be reported (Listing 16.2.4.4, Table 14.1.1.9, Table 14.1.1.10).

7.5.8 Protocol deviations

All the protocol deviations reported during the clinical trial will be listed by subject and summarised; the number and percentage of subjects for each deviation will be reported (Listing 16.2.2.1, Table 14.1.1.11, Table 14.1.1.12).

7.5.9 Medical and dermatological history

All the findings of medical history of all subjects enrolled in the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and listed (Listing 16.2.10.1). The version of the dictionary used for coding will be reported in the clinical study report.

The findings of medical history will be summarised. The number and percentage of subjects with any findings will be presented by PT and SOC (Table 14.1.1.13).

7.5.10 Brief physical examination

Whether the physical examination was performed or not and, if performed, the date of examination will be listed (Listing 16.2.10.2).

7.5.11 Prior and concomitant medications

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE) and listed (Listing 16.2.10.3). The version of the dictionary used for coding will be reported in the clinical study report.

Prior and concomitant medications will be listed and summarized. The number and percentage of subjects with any concomitant medication will be presented by and ATC 4th level (or the higher available ATC level if 4th level is missing) and standardised drug name (Table 14.1.1.14, Table 14.1.1.15).

7.5.12 Concurrent Therapies and Procedures

Non medication concurrent therapies and procedures will be listed (Listing 16.2.10.4).

7.5.13 Subjects study visits

The dates of all subjects study visits will be listed (Listing 16.2.10.5).

7.6 Efficacy analysis

The investigator's global assessment scores for face and trunk will be listed (Listing 16.2.6.1) and summarised using contingency tables for the ITT and PP sets (Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.3, Table 14.2.1.4).

7.7 Subgroup Analyses

No subgroup analysis is planned.

7.8 Treatment compliance and extent of exposure analyses

7.8.1 Treatment compliance

The dispensation date, the weight of the dispensed article, the return date, the weight of the returned article, the number of applied doses, the number of expected doses and compliance rate will be listed separately for face and trunk (Listing 16.2.5.1, Listing 16.2.5.2).

Descriptive statistics will be used to summarize the test article compliance at each visit and overall for the ITT and PP sets separately for face and trunk. The proportion of compliant (i.e. with a compliance $\geq$ 80%) and non-compliant (i.e. with a compliance $<$ 80%) subjects will be summarized by table of frequencies at each visit and overall for the ITT and PP sets separately for face and trunk (Table 14.2.2.1, Table 14.2.2.2, Table 14.2.2.3, Table 14.2.2.4).

7.8.2 Extent of exposure

The date/time of first and last application, the total amount of test article used (calculated as number of grams applied for each subject from the weights of the returned test articles) and the mean daily amount of test article applied (calculated as the total amount of test article used divided by the number of days of treatment) will be listed (Listing 16.2.5.3).

Descriptive statistics will be used to summarize exposure to the test article at each visit and overall for the ITT, PP and Safety sets (Table 14.2.2.5, Table 14.2.2.6, Table 14.2.2.7).

7.8.3 Treated areas and dose adjustments

The treated areas and any dose adjustments will be listed (Listing 16.2.5.4).

7.8.4 Dosing

The date/time of facial application and truncal application, the trunk areas to be treated and the percent BSA of truncal acne to be treated wil be listed at each visit (Listing 16.2.5.5).

7.9 Safety analysis

All safety analyses will be performed on subjects of the Safety set. Subjects will be analysed according to the treatment they actually received.

7.9.1 Local Skin Reactions (LSRs)

LSRs (telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus) will be listed separately for face and trunk (Listing 16.2.9.1, Listing 16.2.9.2) and summarized separately for face and trunk by the frequency of each individual LSR and severity at each visit (Table 14.3.5.1, Table 14.3.5.2).

7.9.2 Adverse events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and listed. The version of the dictionary used for coding will be reported in the clinical study report.

Individual TEAEs (i.e. all the all AEs occurring or worsening after the first dose of the test article) will be listed (Listing 16.2.7.1).

TEAEs will be summarised as follows:

- The number and percentage of subjects with any TEAE and the number of TEAEs will be presented overall (Table 14.3.1.1) and by SOC and PT (Table 14.3.1.2);
- The number and percentage of subjects with any TEAE by relationship and the number of TEAEs by relationship will be presented (Table 14.3.1.1);
- The number and percentage of subjects with any TEAE related to the IMP and the number of TEAEs related to the IMP will be presented by SOC and PT (Table 14.3.1.3);
- The number and percentage of subjects with any TEAE by severity and the number of TEAEs by severity will be presented overall (Table 14.3.1.1) and by SOC and PT (Table 14.3.1.4);
- The number and percentage of subjects with any TEAE leading to discontinuation and the number of TEAEs leading to discontinuation will be presented (Table 14.3.1.1).

Serious TEAEs will be summarised as follows:

- The number and percentage of subjects with any Serious TEAE and the number of Serious TEAEs will be presented overall (Table 14.3.1.1) and by SOC and PT (Table 14.3.1.5);
- The number and percentage of subjects with any Serious TEAE by relationship and the number of Serious TEAEs by relationship will be presented (Table 14.3.1.1);
- The number and percentage of subjects with any Serious TEAE related to the IMP and the number of Serious TEAEs related to the IMP will be presented by SOC and PT (Table 14.3.1.6);
- The number and percentage of subjects with any Serious TEAE leading to discontinuation and the number of Serious TEAEs leading to discontinuation will be presented (Table 14.3.1.1).
- The number and percentage of subjects with any Serious TEAE leading to death and the number of Serious TEAEs leading to death will be presented (Table 14.3.1.1).

All Serious TEAEs will be listed and all TEAEs leading to discontinuation will be listed (Table 14.3.2.1).

7.9.3 Vital signs

Vital signs will be listed (Listing 16.2.9.3) and summarised. Descriptive statistics (mean, standard deviation, CV%, minimum, median and maximum) will be presented (Table 14.3.5.3).

7.9.4 Pregnancy tests

The results of pregnancy at Baseline, LTF-Month 6 and EOS test will be listed (Listing 16.2.8.1).

7.10 Interim Analyses

No interim statistical analysis is planned.

8. ANALYSIS DATASETS

Analysis datasets will be created according to the ADaM model of CDISC (6).

9. REFERENCES

1. ICH Topic E9: Statistical principles for clinical trials. CPMP/ICH/363/96
2. Guidance for Industry - Acne Vulgaris: Developing Drugs Treatment - Draft version, September 2005
3. CB-03-01/27. A Phase 3, An Open-Label, Long-Term Extension Study To Evaluate The Safety Of Cortexolone 17A-Propionate (Cb-03-01) Cream, 1% Applied Twice Daily In Subjects With Acne Vulgaris. Cassiopea SpA, September 9, 2015
4. Celasco G, Moro, L, Bozzella R, Ferraboschi P, Bartorelli L, Quattrocchi C, Nicoletti F. Biological profile of cortexolone 17α-propionate (CB-03-01), a new topical and peripherally selective androgen antagonist. Arzneim.-Forsch. 2004; 54, 881-886
5. SAS/STAT® 9.3 User's Guide
6. Analysis Data Model (ADaM) - Implementation Guide - Final version 1.0, December 17, 2009

10. APPENDICES

Appendix 1. Section 14 - Tables Shells

Appendix 2. Section 16.2 - Individual Subject Data Listings Shells