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

PROTOCOL NUMBER:	CB-03-01/27
[redacted]PROJECT NUMBER:	171-7151-305
REGULATORY FILING NUMBER:	IND #112,137
EUDRACT NUMBER	2015-002637-21
ORIGINAL PROTOCOL:	September 9, 2015
FILENAME:	CB-03-01_27_pro_09Sep2015_v1.0
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24 Hour Emergency Telephone Number

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PROTOCOL APPROVAL

The following individuals approve version 1.0 of the CB-03-01/27 protocol dated September 9, 2015. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

Cassiopea S.p.A. Representative(s):

[redacted]

Date: 11 Sept 2015

Date: 11 Sept 2015

Date: 15 SEP 2015

Date: 10 - Sept - 2015

Date: 10 Sep 2015

Date: 10-Sep-2015

Date: 21-Sept-2015

STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to Cassiopea S.p.A., the Sponsor.

I have read this protocol and agree that it contains all the details necessary to conduct the study as described. I will conduct this study following this protocol and will make a reasonable effort to complete the study in the time noted.

I will provide the contents of this protocol to study staff under my direct supervision that need to know the contents to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the test articles. I will provide the contents of the protocol to the responsible Institutional Review Board(s). These disclosures may be made; providing the contents are not used in any other clinical study and they are not disclosed to any other person or entity without prior written consent from Cassiopea S.p.A. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to Cassiopea S.p.A. of any such disclosure.

I understand the study may be terminated or enrollment suspended at any time by Cassiopea S.p.A., with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

Any additional information added to this protocol is also confidential and proprietary to Cassiopea S.p.A. and must be treated in the same manner as the contents of this protocol.

_____
Printed Name of Principal Investigator

_____ _____
Investigator Signature Date

Protocol number: CB-03-01/27 Site number: ____

Version: 1.0

Date of final version: September 9, 2015

PROTOCOL SYNOPSIS

Title	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
Study Type	Phase 3
Test Article / Investigational Product	CB-03-01 cream containing 1% cortexolone 17α-propionate
Study Objective	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.
Study Design	Multicenter, open label study.
Treatment Groups	All subjects will apply CB-03-01 cream, 1% twice daily (BID) to the entire face and, if designated by investigator AND desired by subject, truncal acne for an additional nine months of treatment.
Duration of Treatment	9 additional months. All subjects will apply the active medication (CB-03-01 cream, 1%) twice daily (BID) for an additional nine months of treatment (for a total of up to 12 months; 0 or 3 months in the Phase 3 pivotal study [CB-03-01/25 and CB-03-01/26] and an additional 9 months in this open-label long-term extension study). Treatment on face and/or trunk may be discontinued if/when acne clears (achieves an IGA of grade 0 or "minimal" grade 1) and re-instated if/when acne worsens (IGA ≥2) according to the assessment of the investigator for each respective treatment area.
Duration of Study	Each subject's participation will be for nine (9) months.
Study Population	Male and female subjects 9 years or older who were enrolled and completed participation in one of the Phase 3 pivotal studies [CB-03-01/25 and CB-03-01/26].
Total Number of Subjects	Approximately 600 subjects will be enrolled in this trial 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 will be competitive; upon enrollment of about 600 subjects in this study, the option for rollover will not be offered to other subjects in the Phase 3 pivotal studies (CB-03-01/15 and CB-03-01/26), even if those subjects are eligible.
Number of Sites	Approximately 78 sites that are participating in either Phase 3 pivotal study [CB-03-01/25 and CB-03-01/26] will also participate in this study.

Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Subject must have been 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 (Visit 4-Pivotal). 2. Subject agrees to treat his/her facial acne and truncal acne (if designated by investigator AND desired by subject) during the nine month study period per protocol. Note: Subjects who are clear (IGA=0) at Visit 4-Pivotal are also eligible for this study. 3. Females must be post-menopausal[1], surgically sterile[2], or using highly effective birth control methods.[3,4] Women of childbearing potential (WOCBP)[5] must have a negative urine pregnancy test (UPT) at Visit 4-LTF (or Visit 4-Pivotal, if the visits occur on the same day). 4. Subject has provided written informed consent/assent. A subject under 18 years of age must provide written informed assent and be accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at that time to continue study participation. 5. Subject is willing to comply with study instructions and return to the clinic for required visits.
Exclusion Criteria	A subject is ineligible to enter the study if he/she meets one or more of the following criteria: 1. Subject is pregnant, lactating, or is planning to become pregnant during the study. 2. Subject has any skin pathology or condition that could interfere with the safety evaluation of the test products or requires the use of interfering topical or systemic therapy (see Section 8.1: Prohibited Medications and Therapies). 3. Subject has any condition which, in the investigator's opinion, would make it unsafe or unsuitable for the subject to participate in this research study. 4. Subject plans to use any <u>other</u> investigational drug or device during participation in this study.

[1] Defined as amenorrhea greater than 12 consecutive months.
[2] Hysterectomy, bilateral tubal ligation (at least six months prior to study entry), or bilateral oophorectomy.
[3] Highly effective contraception includes a) total abstinence, b) oral, injected, or implanted hormonal methods of contraception for at least two complete cycles (i.e.; eight to twelve weeks) prior to it being considered highly effective, c) intrauterine device (IUD) for at least one week prior to it being considered highly effective, d) partner vasectomy (performed at least six months prior to study entry), or e) double barrier methods of contraception [barrier methods include male or female condom, diaphragm with spermicidal foam/gel/film/vaginal suppository, cervical cap with spermicides, or contraceptive sponge].
[4] WOCBP taking hormonal therapy for any reason must not change their dosing regimen during the study.
[5] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal.

	5. Subject, and parent/guardian if required, is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function. 6. Subject may be unreliable for the study including subjects who engage in excessive alcohol intake or drug abuse, or subject who is unable to return for scheduled follow-up visits. 7. Subject has known hypersensitivity or previous allergic reaction to any of the active or inactive components of the test article. 8. Subject is or plans to use any topical anti-acne preparations (excluding CB-03-01 cream) or procedures on the face (or trunk, if applicable) or any systemic anti-acne medications (as detailed in Section 8.1: Prohibited Medications and Therapies) during the study.
Study Procedures	The study will consist of a Baseline Visit, follow-up visits at LTF-Months 1, 3, 6, and 9, and follow-up phone calls at LTF-Months 4.5 and 7.5. For subjects in the Phase 3 pivotal studies randomized to active (CB-03-01 cream, 1% twice daily), the total treatment period will be 12 (3+9) months; whereas for those subjects in the Phase 3 pivotal studies randomized to vehicle, the total treatment period will be 9 (0+9) months. 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. During the LTF study, subjects will treat facial acne per protocol for nine months. Treatment of truncal acne is optional and will be discussed by the investigator and subject (see Section 10.3). If truncal acne is to be treated, the subject must continue to treat the designated treatment area for the remainder of the study as detailed in Section 6.2. Treatment on face and/or trunk for a subject may be discontinued if/when acne is under successful control (achieves an IGA of grade 0 or "minimal" grade 1) and re-instated if/when acne worsens (IGA ≥2) according to the assessment of the investigator for each respective treatment area. Subjects must be seen by the investigator via a scheduled or unscheduled visit to change (i.e., restart or stop) test article dosing. Acne will be managed per protocol as detailed in Section 6.2 and Section 8.2. Visit 4-LTF (Baseline): At Visit 4-LTF, study staff will explain the study procedures and an informed consent/assent must be signed prior to the initiation of any study-related procedures. At this visit, inclusion/exclusion criteria will be reviewed to determine subject eligibility. Demographics and medical/dermatological history data will be used from the Phase 3 pivotal study. A brief physical examination including vital signs and a UPT (if applicable) will be performed. Note: 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. IGA for the face and local skin reactions (LSRs) [pre-application for the face] performed during the EOS Visit of the Phase 3 pivotal study (Visit 4-Pivotal) will be used as Baseline data. Treatment of truncal acne will be discussed by the investigator and subject. If the subject desires, the truncal treatment area will be defined and agreed upon by the investigator and the subject, with the percent body surface area (BSA) to be treated recorded. If the investigator

	and subject designate a treatment area for truncal acne, the subject must continue to treat this area for the duration of the study with dosing adjustments per protocol as detailed in Section 6.2. If the investigator and subject do not designate a treatment area for truncal acne at this visit, one may be designated at subsequent visits (e.g., if acne worsens in the truncal area); however, once treatment begins in such truncal treatment area, the subject must continue to treat this area for the remainder of the study as detailed in Section 6.2. If applicable, IGA and LSRs [pre-application] for the trunk will also be assessed at this visit. Ongoing concomitant medications and procedures will be reviewed. The subject (and parent/guardian, if applicable) will be instructed on how to apply the investigational test article (ITA). ITA and subject diary will be dispensed. The first dose will be applied during this visit under supervision of the investigator, except for those subjects with clear facial acne and no truncal acne. LSRs post-application (for both face and trunk separately, as applicable) and adverse events (AEs) will be assessed. The subject will be scheduled for the first follow-up visit. NOTE: If a subject's acne is totally clear (i.e., IGA=0) on face and/or trunk, the subject will not receive or apply the ITA at home for the first month of the study and be reassessed at Visit 5 or earlier (after an unscheduled visit), if acne worsens (be it on the face and/or the trunk) before Visit 5. Visits 5 (LTF Month 1), 6 (LTF Month 3), and 8 (LTF Month 6): Subjects will return to the clinic. IGA, LSRs, and AEs will also be assessed. Concomitant medications and procedures and ITA compliance will be reviewed. A UPT (if applicable) will be performed at Visit 8. Assessment of the subject's acne will be made on face and trunk to determine if the subject requires on-going therapy or if treatment needs to be started (i.e., for subjects with an IGA=0 at Baseline [Visit 4-LTF]) or restarted (after a previous discontinuation due to acne clearing). Based on this determination, ITA and a subject diary will be dispensed/returned (as required). For subjects starting treatment at this visit, the first dose of the ITA will be applied under supervision of the investigator. The subject will be scheduled for a follow-up visit (at Visit 5 and Visit 6) or end of study (EOS) visit (at Visit 8). Visit 7: Phone Call 1 (LTF Month 4.5) and Visit 9: Phone Call 2 (LTF Month 7.5): The site staff will contact the subject by telephone to review any changes in concomitant medications and procedures as well as test article compliance. Site staff will query the subject about any AEs and will confirm the next appointment. In the event there is: a) improving or worsening of the subject's acne such that the treatment may be discontinued or restarted, respectively, OR b) a concern regarding an AE or the subject's progress based upon the Phone Call visit, the subject may be seen in the clinic as an unscheduled visit at the discretion of the investigator. However, to change (i.e., restart or stop) test article dosing on either treatment area (face and/or trunk), the subject must be seen and evaluated in person by the investigator or designee. Visit 10 (Month 9): End of Study (EOS) Visit & Early Termination. Subjects will return to the clinic for the final visit. UPT (if applicable) will be performed. IGA, LSRs, and AEs will be assessed. Concomitant medications

	and procedures will be reviewed. ITA and subject diary will be returned. The subject will exit the study. Unscheduled Visit: [If/As Needed]. *Note: Subjects must be seen by the investigator via a scheduled or an unscheduled visit to change (i.e., restart or stop) test article dosing on either treatment area (face and/or trunk).* Subjects may return to the clinic at the discretion of the investigator. LSRs, AEs, and any changes in concomitant medications and procedures will be assessed, as needed. In addition, IGA, to document acne improvement/clearance (i.e., achieves an IGA of grade 0 or "minimal" grade 1) or significant worsening (IGA ≥2), shall also be assessed to support treatment modifications. ITA will be dispensed/returned (as required). The next regular follow-up visit will be confirmed prior to the end of the unscheduled visit.
Study Measurements	***Safety*** will be assessed by the investigator via the evaluation of local and systemic AEs at each visit/phone call. LSRs including telangiectasia, skin atrophy, striae rubrae, erythema, edema, and scaling/dryness will be assessed by the investigator for each treatment area (face and trunk) using a five-point ordinal scale from 0=none to 4=severe at each visit (Visit 4-LTF [post-application, if applicable], and Visits 5, 6, 8, and 10, and any Unscheduled Visits, as needed). Subjects will be asked to rate the severity of stinging/burning and pruritus for each treatment area (face and trunk) using a four-point scale from 0=none to 3=severe at each visit (Visit 4-LTF [post-application, if applicable], and Visits 5, 6, 8, and 10, and any Unscheduled Visits, as needed). ***Efficacy*** will be assessed by the investigator using an IGA. 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 will be used as Baseline data. If treatment of the trunk begins post-Visit4-LTF, the Baseline data will be assessed at the visit where treatment is first applied. Investigator's Global Assessment (IGA): Overall severity of acne using a five-point scale from 0=clear to 4=severe will be conducted at Visits 5, 6, 8, and 10 for each treatment area (face and trunk) and any Unscheduled Visits, as needed. This is a static morphological scale that refers to a point in time and not a comparison to Baseline.
Study Endpoints	**Safety Endpoints:** • 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. **Efficacy Endpoints:**

	• 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).
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 will 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).
Statistical Methods	All statistical processing will be performed using SAS® 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. **Study Sets:** Subjects who complete 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 Safety set will include all subjects who received at least one application of the test article. The intent-to-treat (ITT) set will include all enrolled subjects. The per-protocol (PP) set will be a subset of the ITT set and will include subjects who completed the study without any significant protocol deviations. The analysis of safety will be conducted on the Safety set. The analysis of efficacy will be conducted on both the ITT and PP sets. **Safety Analyses:** *Extent of Exposure* Descriptive statistics will be used to summarize exposure to test article for the Safety, ITT, and PP sets. The total amount of test article used (grams applied) will be calculated for each subject from the weights of the returned test articles. The mean daily amount of test article applied (total amount of test article used/number of days of treatment) will be calculated for each subject. The number of applications and days dosed for each treatment area (face and/or trunk from Subject Diary) will also be summarized.

	Local Skin Reactions (LSRs) LSRs (telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus) will be summarized by the frequency of each individual LSR and severity at each clinic visit for face and trunk, separately. *Adverse Events (AEs)* AEs will be coded using the MedDRA coding dictionary summarized by relationship to test article and severity. **Efficacy Analyses:** *Investigator's Global Assessment* Frequency distributions of IGA scores will be summarized at Baseline (EOS-Pivotal), and LTF Months 1, 3, 6, and 9 for face and trunk, separately.

SCHEDULE OF EVENTS

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 will have an overall exposure to CB-03-01 cream, 1% of 3 months and others will have 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 will be 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 will be 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 will be 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) will be used as pre-application data for face. LSRs [pre-application] will be assessed for trunk at Visit 4-LTF. After ITA application in the clinic, LSRs will be assessed post-application (Visit 4-LTF) for face and trunk, as applicable.
[10] Any ongoing concomitant medications and procedures will be 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.

ABBREVIATIONS

AE	Adverse Event
BID	Twice a day
BSA	Body Surface Area
CB-03-01	Cortexolone 17α-propionate
CLIA	Clinical Laboratory Improvement Amendments
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CV%	Percent Coefficient of Variation
EDC	Electronic Data Capture
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITA	Investigational Test Article
ITT	Intent-to-Treat
IUD	Intrauterine Device
LSR	Local Skin Reaction
LTF	Long-Term Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-Counter
PP	Per-Protocol
QA	Quality Assurance
RX	Prescription
SAE	Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
[redacted]	[redacted]
UPT	Urine Pregnancy Test
WOCBP	Women of Childbearing Potential

TABLE OF CONTENTS

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 [1].

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. 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%.

3. OBJECTIVE

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.

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 will apply 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 will be 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.

Subjects will treat facial acne per protocol for nine months. Treatment of truncal acne will be discussed by the investigator and subject. If the subject desires, the truncal treatment area will be defined and agreed upon by the investigator and the subject. If the investigator and subject designate a treatment area for truncal acne, the subject must continue to treat this area for the duration of the study per protocol as detailed in Section 6.2. If the investigator and subject do not designate a treatment area for truncal acne at Baseline [Visit 4-LTF], one may be designated at subsequent visits (e.g., if acne worsens in the truncal area), but once treatment begins in such treatment area, the subject must continue to treat this area per protocol for the remainder of the study.

Treatment on the face and/or trunk may be discontinued if/when acne clears (achieves an IGA of grade 0 or "minimal" grade 1) and re-instated if/when acne worsens (IGA ≥2), according to the assessment of the investigator for each respective treatment area (i.e., face and trunk). Note: Subjects must be seen by the investigator via a routinely scheduled study visit or an unscheduled visit to change (i.e., restart or stop) test article dosing on either treatment area (i.e., face and trunk).

Subjects (approximately 600) will be rolled over from the Phase 3 pivotal studies [CB-03-01/25 and CB-03-01/26] into this long-term, safety 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).

5. STUDY POPULATION

5.1 Subject Eligibility

To be included in the study, subjects must meet the following inclusion and none of the exclusion criteria.

5.1.1 Inclusion Criteria

1. Subject must have been 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 (Visit 4-Pivotal).
2. Subject agrees to treat his/her facial acne and truncal acne (if designated by investigator AND desired by subject) during the nine month study period per protocol. Note: Subjects who are clear (IGA=0) at Visit 4-Pivotal are also eligible for the study.

3. Females must be post-menopausal[6], surgically sterile[7], or using highly effective birth control methods.[8,9] Women of childbearing potential (WOCBP)[10] must have a negative urine pregnancy test (UPT) at Visit 4-LTF (or Visit4-Pivotal, if the visits occur on the same day).
4. Subject has provided written informed consent/assent. A subject under 18 years of age must provide written informed assent and be accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at that time to continue study participation.
5. Subject is willing to comply with study instructions and return to the clinic for required visits.

5.1.2 Exclusion Criteria

1. Subject is pregnant, lactating, or is planning to become pregnant during the study.
2. Subject has any skin pathology or condition that could interfere with the safety evaluation of the test products or requires the use of interfering topical or systemic therapy (see Section 8.1: Prohibited Medications and Therapies).
3. Subject has any condition which, in the investigator's opinion, would make it unsafe or unsuitable for the subject to participate in this research study.
4. Subject plans to use any other investigational drug or device during participation in this study.
5. Subject, and parent/guardian if required, is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
6. Subject may be unreliable for the study including subjects who engage in excessive alcohol intake or drug abuse, or subjects who are unable to return for scheduled follow-up visits.
7. Subject has known hypersensitivity or previous allergic reaction to any of the active or inactive components of the test article.
8. Subject is or plans to use any topical anti-acne preparations (excluding CB-03-01 cream) or procedures on the face (or trunk, if applicable) or any systemic anti-acne

[6] Defined as amenorrhea greater than 12 consecutive months.
[7] Hysterectomy, bilateral tubal ligation (at least six months prior to study entry), or bilateral oophorectomy.
[8] Highly effective contraception includes a) total abstinence, b) oral, injected, or implanted hormonal methods of contraception for at least two complete cycles (i.e., eight to twelve weeks) prior to it being considered highly effective, c) intrauterine device (IUD) for at least one week prior to it being considered highly effective, d) partner vasectomy (performed at least six months prior to study entry), or e) double barrier methods of contraception [barrier methods include male or female condom, diaphragm with spermicidal foam/gel/film/vaginal suppository, cervical cap with spermicides, or contraceptive sponge].
[9] WOCBP taking hormonal therapy for any reason must not change their dosing regimen during the study.
[10] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal.

medications (as detailed in Section 8.1: Prohibited Medications and Therapies) during the study

5.1.3 Subject Withdrawal Criteria

Procedures for handling subjects who are discontinued from the study are described in Section 13.2.

6. TEST ARTICLES AND REGIMEN

6.1 Description

Test article name:	CB-03-01 Cream, 1%
Active ingredient:	Cortexolone 17α-propionate (11-deoxy-hydrocortisone-17α-propionate).
Other ingredients:	Cetyl alcohol, glycerol monostearate, liquid paraffin, propylene glycol, tocopherol, sodium edetate, polysorbate 80, citric acid, purified water.

6.2 Instructions for Use and Application

Subjects will treat facial acne per protocol for nine months. Treatment of truncal acne will be discussed by the investigator and subject. If the subject desires, the truncal treatment area will be defined and agreed upon by the investigator and the subject. If the investigator and subject designate a treatment area for truncal acne, the subject must continue to treat this area per protocol for the duration of the study as detailed below. If the investigator and subject do not designate a treatment area for truncal acne at Baseline (Visit 4-LTF), one may be designated at subsequent visits (e.g., if acne worsens in the truncal area), but once treatment begins in such treatment area, the subject must continue to treat this area per protocol for the remainder of the study.

At the first visit, the subjects will be instructed to wash the area to be treated (entire face and trunk, if applicable) with mild soap and water and then dry the area gently. The study staff will then instruct the subject and parent/guardian (if applicable) on how to dispense the test article, how much of the test article to use, and where to apply the assigned test article. The first application of the test article should be applied in the office at Visit 4-LTF under supervision of the study staff after the treatment areas have been determined, except for those subjects with clear facial acne and no truncal acne. For subjects starting treatment at subsequent visits, the first dose of the test article will be applied at that visit under supervision of the study staff. Typically, for the face, about one (1) gram of the test article will be dispensed onto a fingertip and applied by gently dabbing small amounts of the test article on multiple regions of the face (e.g., forehead, nose, cheeks, chin). Using a fingertip, the test article will be spread to provide a thin, uniform layer of the test article **over the entire face**. In addition, if applicable, subjects who choose (with investigator's approval) to treat truncal acne should apply a thin uniform application of the test article to the

designated area(s) of the trunk (e.g., the shoulders, chest, and/or back). *Note: one (1) gram of cream will cover approximately a 8.5" x 11" (~22 cm x 28 cm) area.*

Subject and parent/guardian (if applicable) will also be provided with a Subject Instruction Sheet (Appendix 1) providing them with instructions on how to use and store the cream at home during the study period. Subjects and parents/guardians (if applicable) will be instructed to apply the test article to the whole face and trunk, if applicable, twice daily (morning and in the evening) for nine additional months. The subject should ideally allow at least eight hours between applications. All subjects should not wash the treated area for at least four hours following test article application and should not apply the test article within four hours prior to any study visit.

If a subject's acne is totally clear (i.e., IGA=0) on face and/or trunk at Visit 4-LTF, the subject will not apply the test article to the area(s) that is clear at home for the first month of the study and be reassessed at Visit 5 or earlier (after an unscheduled visit), if acne worsens (in either area) before Visit 5. If acne is totally clear on the face and the trunk has not been designated for treatment, the subject will not be dispensed the test article at Visit 4-LTF. For subjects whose acne is not totally clear (i.e., IGA>0) at Visit 4-LTF, the subject should apply the test article at home twice daily (morning and evening) as instructed by the study staff.

Over the course of the study, treatment on the face and/or trunk may be discontinued if/when acne clears (achieves an IGA of grade 0 or "minimal" grade 1) and re-instated if/when acne worsens (IGA≥2), according to the assessment of the investigator for each respective treatment area. If treatment is discontinued on face and trunk, all containers of the test article should be collected. If treatment is re-instated, sufficient test article will be dispensed to the subject; previously returned test article should NOT be re-dispensed, rather new containers of the test article will be dispensed as needed to the subject. Note: Subjects must be seen by the investigator via a scheduled or an unscheduled visit to change (i.e., restart or stop) the test article dosing on either treatment area (face and trunk). **If the subject feels that his/her acne has cleared, he/she should continue to apply the test article to the designated treatment area (face and/or trunk) as instructed by the investigator and call the investigator for an unscheduled visit. The subject should NOT change his/her dosing regimen until the investigator has documented acne clearance or significant worsening to support a change in the treatment.**

Subjects will be provided with a Subject Diary (Appendix 2) to record the dates and time of application, along with where the test article was applied. Subjects will be instructed to only apply the test article to the face and/or trunk as instructed by the investigator or designated study personnel. **Note: The dispensing, recording, and application of the test article by the subject may require adult supervision by the subject's parent/guardian.**

Subject and parent/guardian (if applicable) will be instructed to bring all the containers of cream (used and unused) and their completed diaries to each visit. The study staff will

weigh all the returned containers and will record the weights on the appropriate study medication accountability logs and case report forms (CRFs). Test articles that are returned should NOT be re-dispensed to the subject.

Subjects who are not compliant with applying the test article as instructed (determined from subject diaries and/or the weight of test article used) may be discontinued from the study.

6.3 Warnings, Precautions and Contraindications

The test article is for topical use only. Care should be taken to avoid contact with eyes and all mucous membranes. If contact with eyes occurs, rinse thoroughly with water.

Subjects with a known sensitivity to any of the ingredients in the test article should not participate in this study.

Should skin irritation or rash develop, subjects should discontinue use and contact the study site.

In case of accidental ingestion, subjects should contact the investigator immediately.

The effects of the test article in nursing mothers, pregnant women and their unborn children are unknown. WOCBP must not be pregnant or planning a pregnancy during the study period.

7. RANDOMIZATION ASSIGNMENT

There is no randomization assignment in this study. This is an open label, extension study in which all eligible subjects will be treated with CB-03-01 cream, 1% (i.e., the test article). About 600 subjects will be enrolled in this extension study 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 will be competitive; upon enrollment of about 600 subjects in this study, the option for rollover will not be offered to other subjects in the Phase 3 pivotal studies (CB-03-01/15 and CB-03-01/26), even if those subjects are eligible. Enrolled subjects will be provided with labeled test article during the study period, as needed. Subject numbers will be carried over from the Phase 3 pivotal study [CB-03-01/25 or CB-03-01/26].

8. PRIOR AND CONCOMITANT THERAPIES

Current medications taken at the start of this study (Visit 4-LTF) will be recorded on the appropriate CRFs with the corresponding indication. The medications to be recorded include RX and OTC medications (except vitamins and dietary supplements not used to treat a medical condition). All medications taken on a regular basis should be recorded on

the Concomitant Medications form prior to commencing the use of the test article. Any medications that were used prior to the start of this study would have been recorded as part of the Phase 3 pivotal study [CB-03-01/25 or CB-03-01/26].

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health. Non-prohibited chronic therapies being used at Visit 4-LTF may be continued. Any changes in concomitant therapies during the study must be recorded on the Concomitant Therapy form. The reason for any change in concomitant therapies should be evaluated and, if appropriate, reported as, or in conjunction with, an AE.

8.1 Prohibited Medications or Therapies

During the study, subjects must not use the following products and/or procedures on the face or trunk:

- Any other investigational drug or use of any investigational device;
- Light treatments (including artificial tanning devices, blue light, laser, etc.), microdermabrasion, or chemical peels;
- Systemic spironolactone;
- Systemic retinoid therapy;
- All topical acne therapies not allowed per Section 8.2 (e.g. retinoids, azelaic acid, dapsone, etc.).

Other chronic medications being used at the time of Visit 4-LTF can be continued at the discretion of the investigator. The reason for any changes in such concomitant medications and/or therapies should be reported as, or in conjunction with, an AE.

8.2 Allowed Medications or Therapies

All allowed concurrent acne medications and/or therapies must be given IN ADDITION to the test article and NOT IN PLACE of the test article.

During the study, if control of acne is insufficient, the following supplemental products and/or procedures may be used at the discretion of the investigator on the face or trunk:

- Hormonal contraceptives[11];
- Occasional use of systemic antibiotics for acne (not to exceed 12 continuous weeks) or for other medical needs;
- Systemic corticosteroids (for other medical needs);
- Occasional use of intralesional corticosteroid injections for nodular or cystic acne lesions (low dose, e.g., ~2 mg triamcinolone / cc) or for other medical needs;

[11] If hormonal contraception is initiated as concurrent acne therapy, the method of highly effective birth control used at Visit 4-LTF must be continued for at least two complete cycles (i.e., eight to twelve weeks).

- Occasional use of TOPICAL steroids or TOPICAL antibiotics for up to 10 continuous days (for other medical needs) within the treatment area (face and/or trunk);
- TOPICAL anti-acne cleansers (not leave-on products) that have benzoyl peroxide (≤5%) OR salicylic acid (≤2%) as their only active ingredient within the treatment area (face and/or trunk).

Acne Management: The intent of the study is to limit the use of other acne medications to facilitate the safety assessment of long-term use of the investigational test article over a one year period of time. In the event that the study drug does not sufficiently control the subject's acne, the Investigator, at their election, may prescribe select additional medication(s)[12] that can be taken in addition to the investigational test article. Ideally these measures should be used only for brief period(s) of time, if medically necessary, to reasonably control the subject's acne, during the study. These medications are limited to certain products (e.g., topical anti-acne cleansers, oral antibiotics, or intralesional steroid injections for cyst/nodular lesions) as detailed in the list of allowed medications or therapies above.

9. STUDY PROCEDURES

The study will consist of a Baseline Visit, follow-up visits at Months 1, 3, 6, and 9, and follow-up phone calls at Months 4.5 and 7.5. For subjects in the Phase 3 pivotal studies randomized to active (CB-03-01 cream, 1% twice daily), the total treatment period will be 12 (3+9) months; whereas for those subjects in the Phase 3 pivotal studies randomized to vehicle, the total treatment period will be 9 (0+9) months.

During the LTF study, treatment on face and/or trunk for a subject may be discontinued if/when acne is under successful control (achieves an IGA of grade 0 or "minimal" grade 1) and re-instated if/when acne worsens (IGA≥2), according to the assessment of the investigator for each respective treatment area. Subjects MUST be seen by the investigator via a scheduled or unscheduled visit to change (i.e., restart or stop) test article dosing).

Specific activities for each study visit are listed below.

9.1 Visit 4-LTF Baseline (LTF-Day 1) [Visit 4-Pivotal + 3 days]

Informed consent/assent can be obtained up to 45 days before Visit 4-LTF. *Note: Consent/assent for this extension study should not be signed at Baseline of the Phase 3 pivotal study (i.e., Visit 1).* 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.

[12] For US sites: OTC acne cleanser containing 2% salicylic acid or 5% benzoyl peroxide and doxycycline will be provided by the investigator. The subject will be responsible for other additional acne medications that may be prescribed by the investigator.

At this visit, the investigator or designee will:

- Obtain a signed, written informed consent (unless the subject signed a consent within the past 45 days). *Note: A subject under 18 years of age must provide written informed assent and be accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at that time to continue study participation.*
- Confirm the subject meets the inclusion/exclusion criteria.
- Confirm demographics and medical / dermatological history were collected in the Phase 3 pivotal study (Visit 1-Pivotal).
- Review any ongoing concomitant medications and procedures.
- Perform a brief physical exam (including vital signs, height, and weight).
- Perform a UPT for all WOCBP (see Section 5.1 for definition). The results must be negative for the subject to be enrolled. *Note: 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.*
- Confirm that an IGA was performed and LSRs were assessed for the face at Visit 4-Pivotal.
- Discuss with the subject if truncal acne will be treated. If applicable, identify the truncal treatment area and record the percent BSA of the truncal treatment area (see Section 10.3). *Note: If the investigator and the subject designate a treatment area for truncal acne, the subject must continue to treat this area per protocol for the duration of the study as detailed in Section 6.2.*
- Prior to the first application of the test article, for the trunk (if applicable).
    - Perform IGA (see Section 10.1); and
    - Perform LSR assessment (see Section 10.2).
- Determine if the subject requires ongoing therapy based on IGA scores of the face and trunk. *Note: If a subject's acne is totally clear (IGA=0) on face and/or trunk, the subject will not receive or apply the ITA for the first month of the study and will be reassessed at Visit 5 or earlier (after an unscheduled visit), if acne worsens (be it on the face and/or the trunk) before Visit 5.*
- Dispense the Subject Instruction Sheet to the subject and parent/guardian (if applicable) (Appendix 1), as required.
- Dispense the Subject Diary to the subject and parent/guardian (if applicable) and provide completion instructions (Appendix 2), as required.
- Weigh and dispense the test article and complete the Study Medication Accountability Log, as required (Appendix 3).
- Instruct the subject and parent/guardian (if applicable) where and how to apply the initial dose of the test article following the procedures in Section 6.2. The first application should occur in the office under supervision of the study staff, except for those subjects with clear facial acne and no truncal acne.

- Record any AEs.
- Assess LSRs post-application for face AND trunk, separately, and as applicable (see Section 10.2).
- Instruct the subject and parent/guardian (if applicable) to apply the test article to the designated treatment areas (i.e., face and/or trunk) twice per day, with at least eight hours between applications.
- Remind the subject that if the subject feels that his/her acne has cleared or significantly worsened (for those subjects with IGA=0), the subject should contact the investigator for an unscheduled visit. *Note: Subjects MUST be seen by the investigator via a scheduled or an unscheduled visit to change (i.e., start or stop) test article dosing on either treatment area (face and trunk).*
- Schedule Visit 5 (LTF-Month 1).

9.2 Visit 5 (LTF-Month 1) [Day 29 ± 10], Visit 6 (LTF-Month 3) [Day 85±15], and Visit 8 (LTF-Month 6) [Day 183±15]

At this visit, the investigator or designee will:

- Observe/query the subject about any changes in his/her health since the previous study visit, including AEs and concomitant medications/therapies, and document the findings.
- Perform a UPT for all WOCBP (see Section 5.1 for definition) (**Visit 8 ONLY**).
- Perform IGA for face AND trunk, separately, and as applicable (see Section 10.1).
- Assess LSRs for face AND trunk, separately, and as applicable (see Section 10.2).
- Determine if the subject requires ongoing therapy or if treatment needs to be (re)started based on IGA scores of the face and trunk. *Note: Treatment on the face and/or trunk may be discontinued if/when acne clears (achieves an IGA of grade 0 or "minimal" grade 1) and re-instated if/when acne worsens (IGA≥2) according to the assessment of the investigator for each respective treatment area. Also, if a treatment area for truncal acne was not identified at Baseline (Visit 4-LTF), one may be designated at a subsequent visit (e.g., if acne worsens in the truncal area), but once treatment begins in such treatment area, the subject must continue to treat the designated area per protocol for the remainder of the study as detailed in Section 6.2.*
- Review test article compliance based on Subject Diary and weights of the test article. Remind the subject to apply the test article to the designated treatment areas (i.e., face and/or trunk) twice per day, with at least eight hours between applications.
- Dispense an updated (or new) Subject Instruction Sheet to the subject and parent/guardian (if applicable) (Appendix 1), if the subject is starting treatment at this visit.
- Collect the old and dispense a new Subject Diary to the subject and parent/guardian and provide completion instructions (Appendix 2), if applicable (i.e., acne treatment on the face and/or trunk shall continue per protocol as detailed in Section

6.2). Any noteworthy discrepancies in the Subject Diary should be queried and documented.

- Collect all previously dispensed test article and complete the Study Medication Accountability Log (Appendix 3).
- Weigh and dispense [only if applicable (i.e., acne treatment on the face and/or trunk shall continue per protocol)] new containers of the test article and complete the Study Medication Accountability Log (Appendix 3). *Note: For subjects that were totally clear (IGA=0) at Baseline, if their acne on the face and/or trunk remains totally clear (IGA=0), then do not dispense the test article. If treatment shall not continue per protocol as detailed in Section 6.2, collect all containers of the test article. PREVIOUSLY RETURNED TEST ARTICLE SHOULD NOT BE RE-DISPENSED.*
- If treatment is started for the first time (in this LTF study) on the face and/or trunk,
    - Discuss with the subject if truncal acne will be treated. If applicable, identify the truncal treatment area and record the percent BSA of the truncal treatment area (see Section 10.3). *Note: If the investigator and the subject designate a treatment area for truncal acne, the subject must continue to treat this area per protocol for the remainder of the study.*
    - Instruct the subject and parent/guardian (if applicable) where and how to apply the initial dose of the test article following the procedures in Section 6.2. The first application should occur in the office under supervision of the study staff.
    - Record any AEs.
    - Instruct the subject and parent/guardian (if applicable) to apply the test article to the designated treatment areas (i.e., face and/or trunk) twice per day, with at least eight hours between applications.
- Remind the subject that if the subject feels that his/her acne has cleared or significantly worsened (for those subjects with IGA=0), the subject should contact the investigator for an unscheduled visit. Acne will be managed per Section 6.2 and Section 8.2. *Note: Subjects MUST be seen by the investigator via a scheduled or an unscheduled visit to change (i.e., start or stop) test article dosing on either treatment area (face and trunk).*
- Schedule follow-up visit (at Visit 5 and 6) or an end of study (EOS) visit (at Visit 8).

9.3 Visit 7: Phone Call 1 (LTF-Month 4.5) [Day 137±15] and Visit 9: Phone Call 2 (LTF-Month 7.5) [Day 228±15]

The investigator or designee will contact the subject by telephone to:

- Review any changes in his/her health, with the subject or parent/guardian (as appropriate), since the previous study visit, including AEs and concomitant medications/therapies, and document the findings.
- Review test article compliance.
- Emphasize need to maintain the Subject Diary daily with each application.

- In the event that either of the following occur prior to the next scheduled visit, the subject may be seen in the clinic as an unscheduled visit at the discretion of the investigator:
  - Improving (appears to have achieved an IGA of grade 0 or "minimal" grade 1) or worsening (IGA≥2 after treatment was stopped) of the subject's acne such that the treatment may be discontinued or restarted, respectively; OR
  - A concern regarding an AE or the subject's progress; OR
  - Other item of note from the investigator's perspective.
- *Note: Subjects MUST be seen by the investigator via a scheduled or an unscheduled visit to change (i.e., start or stop) test article dosing on either treatment area (face and trunk).*
- In the event an in-office visit is required, the site should schedule an unscheduled visit for evaluation in a timely fashion.
- Confirm the next scheduled visit.

9.4 Visit 10 (LTF-Month 9) [Day 274 ± 21]: EOS & Early Termination

At this visit, the investigator or designee will:

- Observe/query the subject about any changes in his/her health since the previous study visit, including AEs and concomitant medications/therapies, and document the findings.
- Perform a UPT for all WOCBP (see Section 5.1 for definition).
- Perform IGA for face AND trunk, separately, as needed (see Section 10.1).
- Assess LSRs for face AND trunk, separately, as needed (see Section 10.2).
- Review and collect the Subject Diary. Any noteworthy discrepancies in the diary should be queried and documented.
- Collect and weigh all used and unused test article and complete the Study Medication Accountability Log, as required (Appendix 3).
- Complete the End of Study Form and discharge the subject from the study.

9.5 Unscheduled Visit

The subject may be seen in the clinic as an unscheduled visit at the discretion of the investigator in the event there is (a) improving or worsening of the subject's acne such that the treatment may be discontinued or restarted, respectively, or (b) a concern regarding an AE or the subject's progress based upon the Phone Call visit.

Subjects MUST be seen by the investigator via an unscheduled visit to change (i.e., start or stop) test article dosing on either treatment area (face and trunk).

At this visit, the investigator or designee will:

- Observe/query the subject about any changes in his/her health since the previous study visit, including AEs and concomitant medications/therapies, and document the findings.

- Perform IGA for face AND trunk, separately, as needed (see Section 10.1).
- Assess LSRs for face AND trunk, separately, as needed (see Section 10.2).
- Determine if the subject requires ongoing therapy or if treatment needs to be (re)started based on IGA scores of the face and trunk. *Note: Treatment on the face and/or trunk may be discontinued if/when acne clears (achieves an IGA of grade 0 or "minimal" grade 1) and re-instated if/when acne worsens (IGA≥2) according to the assessment of the investigator for each respective treatment area. Also, if a treatment area for truncal acne was not identified at Baseline (Visit 4-LTF), one may be designated at a subsequent visit (e.g., if acne worsens in the truncal area), but once treatment begins in such treatment area, the subject must continue to treat the designated area per protocol for the remainder of the study as detailed in Section 6.2.*
- Review test article compliance based on Subject Diary and weights of the test article. Remind the subject to apply the test article to the designated treatment areas (i.e., face and/or trunk) twice per day, with at least eight hours between applications.
- Dispense an updated (or new) Subject Instruction Sheet to the subject and parent/guardian (if applicable) (Appendix 1), as required.
- Collect the old and dispense a new Subject Diary to the subject and parent/guardian and provide completion instructions (Appendix 2), if applicable (i.e., acne treatment on the face and/or trunk shall continue per protocol). Any noteworthy discrepancies in the Subject Diary should be queried and documented.
- Collect all previously dispensed test article and complete the Study Medication Accountability Log (Appendix 3).
- Weigh and dispense [only if applicable (i.e., acne treatment on the face and/or trunk shall continue per protocol)] new containers of the test article and complete the Study Medication Accountability Log (Appendix 3). *Note: If treatment shall not continue per protocol as detailed in Section 6.2, collect all containers of the test article. PREVIOUSLY RETURNED TEST ARTICLES SHOULD NOT BE RE-DISPENSED.*
- If treatment is started for the first time (in this LTF study) on the face and/or trunk,
    - Discuss with the subject if truncal acne will be treated. If applicable, identify the truncal treatment area and record the percent BSA of the truncal treatment area (see Section 10.3). *Note: If the investigator and the subject designate a treatment area for truncal acne, the subject must continue to treat this area per protocol for the remainder of the study as detailed in Section 6.2.*
    - Instruct the subject and parent/guardian (if applicable) where and how to apply the initial dose of the test article following the procedures in Section 6.2. The first application should occur in the office under supervision of the study staff.
    - Record any AEs.

- Instruct the subject and parent/guardian (if applicable) to apply the test article to the designated treatment areas (i.e., face and/or trunk) twice per day, with at least eight hours between applications.

- Remind the subject that if the subject feels that his/her acne has cleared or significantly worsened (for those subjects with IGA=0), the subject should contact the investigator for a scheduled or an unscheduled visit. Acne will be managed per Section 6.2 and Section 8.2. *Note: Subjects MUST be seen by the investigator via an unscheduled visit to change (i.e., start or stop) test article dosing on either treatment area (face and trunk).*
- Confirm the next scheduled visit.

10. CLINICAL EVALUATIONS

The following clinical evaluations will be 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.

10.1 Investigator's Global Assessment (IGA)

Overall severity of acne using a five-point scale from 0=clear to 4=severe will be 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 will be used as Baseline data.

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.

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

10.2 Local Skin Reactions (LSRs)

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

- Telangiectasia
- Skin atrophy
- Striae rubrae

A five-point ordinal scale will be used to assess the severity of these reactions (0=none, 1=trace, 2=mild, 3=moderate, and 4=severe).

In addition, the investigator or designee will evaluate 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:

- Erythema
- Edema
- Scaling/dryness

Erythema:

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:

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:

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
4	Severe – coarser scaling involving more than 2/3 of the treatment area or limited areas of very coarse scaling

In addition, subjects will be 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:

- Stinging/burning
- Pruritus

Stinging/burning:

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):

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 will be 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.

10.3 Truncal Body Surface Area (BSA)

Treatment of truncal acne will be discussed by the investigator and subject. If the subject desires, the truncal treatment area will be defined and agreed upon by the investigator and the subject with the percent BSA to be treated recorded. Percent BSA to be treated will be 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 has been defined, the subject must continue to treat this area for the remainder of the study until the area is 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).

11. PHOTOGRAPHY

Photography documentation is not required in this study. However, the investigator may 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.

Note: Subjects may decline to have photographs taken during the conduct of the study. If a subject initially consents to photographs, then declines further photography, the Sponsor may use the photographs taken under consent for the purposes noted above.

12. LABORATORY TESTS

12.1 Urine Pregnancy Tests (UPTs)

The UPT will be performed at the study site if the site meets 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 will be 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 will report 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 must have a minimum sensitivity of 25 mIU of β-HCG/mL of urine.

13. END OF STUDY CRITERIA

At the end of each subject's participation in the study, the investigator will complete an End of Study form for all completed and discontinued subjects.

13.1 Completion of the Study

Each subject who completes the nine month treatment period and the required study visits (Visits 4-LTF and Visits 5-10) will have completed the study.

13.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

- Whenever the subject or the subject's parent/guardian decides it is in the subject's best interest to be withdrawn, Note: if the subject or parent/guardian decides to withdraw from the study due to an AE then it should be classified as withdrawal due to an AE.
- Whenever the investigator decides it is in the subject's best interest to be withdrawn
- AEs
- Worsening of condition or treatment failure (in the opinion of the investigator)
- Noncompliance
- Pregnancy
- Lost to follow-up
- Sponsor administrative reasons

If a subject withdraws prematurely during the nine month treatment period for any reason, the Visit 10 (EOS) procedures should be completed at that time. When a subject is withdrawn from the study for a treatment-related AE (i.e., possibly, probably or definitely related as defined in Section 14), when possible, the subject should be followed until resolution or stabilization of the AE.

13.3 Study Termination

The study may be terminated by the investigator or the Sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, he or she may stop the study. A study termination by the investigator will be reported to the Sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the Sponsor by the investigator within five (5) working days.

In the event that the Sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

14. ADVERSE EVENT REPORTING

An **adverse event** (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with any drug) and from any route of administration, formulation, or dose, including an overdose.

Information on the medical condition of subjects should begin following the subject's written consent/assent to participate in the study and a medical history should be taken at screening. Other changes in subject health information becomes AE data when the subject begins dosing with the test article and therefore AE data should be collected from the date of the first dose of test article. These data are considered treatment-emergent AEs.

Timely and complete reporting of all AEs assists the contract research organization (CRO) in identifying any untoward medical occurrence, thereby allowing:

1) protection of the safety of study subjects;
2) a greater understanding of the overall safety profile of the test article;
3) recognition of dose-related test article toxicity;
4) appropriate modification of study protocols;
5) improvements in study design or procedures; and
6) adherence to worldwide regulatory requirements.

Test article is defined as a pharmaceutical form of an active ingredient or vehicle/placebo being tested or used as a reference in the study, whether blinded or unblinded. AEs may be either spontaneously reported or elicited during questioning and examination of a subject. All AEs must be completely recorded on the AE CRF. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of test article, or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. If possible, report the outcome of any AE that caused permanent discontinuation or that was present at the end of the study particularly if the AE is considered by the investigator to be treatment-related (i.e., definitely, probably, or possibly related to test article).

14.1 Adverse Event (AE)

All AEs must be recorded on the AE CRF. AEs should be followed to resolution or stabilization (if possible), and reported as serious adverse events (SAEs) if they become serious.

LSRs that have been reported in subjects treated with CB-03-01 creams (0.1%-1% concentration) include (with decreasing frequency) erythema, pruritus, scaling/dryness, skin atrophy, striae rubrae, stinging/burning, edema, and telangiectasia; however most LSRs were typically of minimal to mild severity. No subjects discontinued treatment due to these LSRs.

AEs that have been reported in subjects treated with CB-03-01 creams (0.1-1% concentration) were minimal, typically mild in severity, and most were recovered/resolved without sequelae at the end of the study. Only two AEs in one (1) subject were judged as probably or possibly related to treatment; both of these treatment-related AEs (burning and cold at application site) were mild in severity. Two SAEs have been reported to date; both were not related to treatment and were resolved at the end of the study. In addition, one subject discontinued early from the study due to an AE (urinary tract infection), which was not related to treatment.

The investigator will instruct the subject to report any AEs that may occur during the study. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject's overall condition since the previous visit.

The severity of each AE, as judged by the investigator, will be recorded on the appropriate AE CRF and will be graded according to the following scale:

Mild - The AE is transient and easily tolerated by the subject.

Moderate - The AE causes the subject discomfort and interrupts the subject's usual activities.

Severe - The AE causes considerable interference with the subject's usual activities, and may be incapacitating or life-threatening.

The investigator must determine the relationship of the AE to the test article according to the following categories:

Definite - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage, and reappearance of the event on repeated exposure (re-challenge).

Probable - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage of the test article; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.

Possible - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; but may have been caused by concurrent/underlying illness, other drug, procedure, or other causes.

Unlikely - An event that does not follow a reasonable temporal sequence from administration of the test article; that does not follow a known or expected response pattern to the test article, or most likely was caused by concurrent/underlying illness, other drug, procedure, or other causes, because of their known effects.

Not Related - An event almost certainly caused by concurrent/underlying illness, other drug, procedure, or other causes.

The investigator should categorize the outcome of the AE according to the following categories:

Fatal - Termination of life as a result of an AE.

Not Recovered/Not Resolved - AE has not improved or the subject has not recuperated.

Recovered/Resolved - AE has improved or the subject has recuperated.

Recovered/Resolved with Sequelae - subject recuperated but retained the pathological conditions resulting from the prior disease or injury.

Recovering/Resolving - AE is improving or the subject is recuperating.

Unknown - Not known, not observed, not recorded or subject refused.

The investigator should report the action taken with the test article due to the AE according to the following categories:

Dose Not Changed - An indication that a medication schedule was maintained.

Dose Increased - An indication that a medication schedule was modified by addition; either by changing the frequency, strength or amount.

Dose Reduced - An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength or amount.

Drug Interrupted - An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.

Drug Withdrawn - An indication that a medication schedule was modified through termination of a prescribed regimen of medication.

Not Applicable - Determination of a value is not relevant in the current context.

Unknown - Not known, not observed, not recorded, or refused.

The investigator should report any other action taken due to the AE.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. For the purposes of prescription drug labeling, the term adverse reaction means an undesirable effect, reasonably associated with the use of a drug that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

A **suspected adverse reaction** is any AE for which there is a reasonable possibility that the drug caused the event.

For the purposes of IND (and other national health authority) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

14.2 Serious Adverse Event (SAE)

An event that is serious must be recorded on the AE CRF and on the CRO SAE Report Form, and requires expeditious handling to comply with regulatory requirements.

An AE or suspected adverse reaction is considered "serious" if, in the opinion of either the investigator or Sponsor, it results in any of the following outcomes:

- Death.
- Life-threatening event.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.

- Is an important medical event - defined as a medical event(s) that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events NOT considered to be SAEs are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen, and
- Treatment on an emergency, outpatient basis, for an event not fulfilling any of the definitions of "serious" given above and not resulting in hospital admission.

AEs classified as "serious" by either the investigator or the Sponsor require expeditious handling and reporting to the CRO to comply with regulatory requirements. **All serious AEs, whether related or unrelated to test article, must be immediately reported by telephone to the Medical Monitor and, in the event that he/she is unavailable, to the Project Manager listed on the first page of the protocol.** Written notification of all SAEs should be sent to the Project Manager by email or confirmed facsimile transmission. These include those SAEs listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In this case, the investigator must immediately report the event to the Sponsor. In addition, such information should also be provided to the site's respective IRB per their governing guidelines for SAE reporting.

If only limited information is initially available, follow-up reports are required. Should the investigator become aware of an SAE (regardless of its relationship to test article) that occurs within 30 days after stopping the test article, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to the CRO, if available.

As required, the CRO will notify participating investigators of all suspected adverse reactions that are serious and unexpected. This notification will be in the form of an IND (and other national health authority) safety report of potential serious risks as soon as possible but no later than 15 calendar days after the Sponsor determines that the information is "reportable" according to the criteria listed in 21 CFR Section 312.32. These are:

i) Serious and unexpected suspected adverse reactions,

ii) Findings from other studies including epidemiological studies, pooled analyses, or other clinical studies that suggest a significant risk in humans exposed to the test articles,
iii) Findings from animal or in vitro tests that suggest a significant risk to humans exposed to the test articles or reports of significant organ toxicity at or near the expected human exposure, and
iv) Clinically important increases in the rate of occurrence of serious suspected adverse reactions.

Upon receiving such notices, the investigator must review and retain the notice with the Investigator Brochure and immediately submit a copy of this information to the responsible IRB according to local regulations. The investigator and IRB will determine if the informed consent/assent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of safety updates by the investigator to Health Authorities should be handled according to local regulations.

14.3 Pregnancy

WOCBP (see Section 5.1 for definition) must have a negative UPT prior to study enrollment and must use a highly effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject and parent/guardian must sign an informed consent/assent form documenting this discussion.

During the study, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period).

WOCBP enrolling into the study must have a pregnancy test prior to study therapy, and at EOS. The study therapy must be withheld until the results of laboratory pregnancy testing are known, and a negative UPT must be confirmed to continue in the trial. If pregnancy is confirmed during screening, the subject must not receive test article and must not be enrolled in the study.

If a subject or investigator suspects that a subject may be pregnant at any time during the study, the test article must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not apply further test article and must be discontinued from the study.

If following initiation of study treatment, it is subsequently discovered that a trial subject was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the Medical Monitor of this event, and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to the CRO. The

investigator must notify the IRB of any pregnancy associated with the study therapy and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated, including counseling of the subject by the investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the investigator must report to the CRO, on the appropriate CRO pregnancy surveillance form(s), any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs (or SAEs, if they fulfill the SAE criteria). Abortion, whether accidental, therapeutic, or spontaneous should be reported as an SAE. Offspring should be followed for a minimum of eight weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to the test article(s) should be recorded as an SAE and details documented in the pregnancy surveillance form.

15. BLINDING/UNBLINDING

This study is an open label study. There is no blinding of the test article.

16. CLINICAL SUPPLIES

16.1 Test Article Information

Test articles will be packaged and labeled by the Sponsor or designee. Detailed information on the packaging/labeling, storage and preparation, dispensing, accountability etc. is included in Appendix 2.

16.2 Supplies Provided by CRO

- EDC (e.g. access to e-CRFs, etc.)
- Subject Diaries
- Source document draft templates
- Site regulatory binder
- UPT kits
- Weighing scales (if necessary)
- Medications for Additional Acne Management: OTC acne cleanser containing 2% salicylic acid or 5% benzoyl peroxide and doxycycline (for US sites only)

16.3 Supplies Provided by Investigator

- Urine collection containers for UPTs

17. STATISTICAL CONSIDERATIONS

17.1 Sample Size

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 will 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).

17.2 Endpoints

17.2.1 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.

17.2.2 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).

17.3 Statistical Methods

All statistical processing will be performed using SAS® 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.

Subjects who complete 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 Safety set will include all subjects who received at least one application of the test article. The intent-to-treat (ITT) set will include all enrolled subjects. The per-protocol (PP) set will be a subset of the ITT set and will include subjects who completed the study without any significant protocol deviations. The analysis of safety will be conducted on the Safety set. The analysis of efficacy will be conducted on both the ITT and PP sets.

17.3.1 Safety Analyses

Extent of Exposure
Descriptive statistics will be used to summarize exposure to test article for the Safety, ITT, and PP sets. The total amount of test article used (grams applied) will be calculated for each subject from the weights of the returned test articles. The mean daily amount of test article applied (total amount of test article used/number of days of treatment) will be calculated for each subject. The number of applications and days dosed for each treatment area (face and/or trunk from Subject Diary) will also be summarized.

Local Skin Reactions (LSRs)
LSRs (telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus) will be summarized by the frequency of each individual LSR and severity at each clinic visit for face and trunk, separately.

Adverse Events (AEs)
AEs will be coded using the MedDRA coding dictionary summarized by relationship to test article and severity.

17.3.2 Efficacy Analyses

Investigator's Global Assessment (IGA)
Frequency distributions of IGA scores will be summarized at Baseline (EOS-Pivotal), and LTF Months 1, 3, 6, and 9 for face and trunk, separately.

17.4 Subgroup Analyses

No subgroup analyses are planned.

17.5 Interim Analyses

No interim analysis is planned.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Compliance with Good Clinical Research Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice (GCP) guidelines and with other applicable regulations. The investigator and all study staff will conduct the study in compliance with this protocol. The protocol, informed consent/assent documents, recruitment advertisements and any amendments to these items will have IRB approval prior to study initiation. Voluntary informed consent/assent will be given by every subject and the subject's parent/guardian prior to the initiation of any study-related procedures. The rights, safety, and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their assigned responsibilities.

18.2 Institutional Review Board (IRB)/ Ethics Committee and Informed Consent/Assent

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent/assent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects and the subject's parent/guardian. The investigator should also provide the IRB with a copy of the product labeling, information to be provided to subjects/care givers, and any updates. The investigator will submit documentation of the IRB approval to the CRO.

The IRB approved consent/assent form must include all elements required by FDA (or other national health authority), state, and local country regulations, and may include appropriate additional elements.

The investigator/designee will explain the study to each potential subject and the subject's parent/guardian. The subject must indicate voluntary consent/assent by signing and dating the approved informed consent/assent form. The parent or legal guardian must provide written informed consent for the subject. The investigator must provide the subject with a copy of the consent/assent form, in a language the subject understands.

The investigator will maintain documentation that informed consent/assent was obtained prior to the initiation of any study-specific procedures.

18.3 Protocol Compliance

The IRB approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

18.4 Protocol Revisions

The CRO must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding this study must be sent to the CRO.

New or altered consent/assent forms required by the IRB due to a protocol change must be signed by all subjects and the subject's parent/guardian currently enrolled in the study and must be used for any subsequent subject enrollment.

18.5 Study Monitoring

Representatives of the CRO and/or the Sponsor must be allowed to visit all study sites, to review study records, and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff, and to verify that the investigator, study staff, and facilities remain acceptable for the conduct of the study.

Representatives of government regulatory authorities may also evaluate the study records, source documents, investigator, study staff, and facilities.

The investigator should immediately notify the CRO of any audits of this study by any regulatory agency and must promptly provide copies of any audit reports.

18.6 Case Report Form (CRF) Requirements: Electronic Data Capture (EDC)

The study will utilize validated 21CFR Part 11 compliant EDC software to collect CRF data. All requested information must be entered on the CRFs in the areas provided in a timely manner. When changes or corrections are made in the CRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change, and the reason for the change. Only individuals listed on the Delegation of Responsibilities Log with responsibility for CRF completion may make entries on the CRFs. Usernames and passwords will be provided to each authorized user to allow access to the training module. Access to additional features and functions will not be enabled until the user has successfully completed the training.

The investigator or physician sub-investigator must electronically sign and date each subject's CRF. Individuals who will be providing electronic signatures must first submit documentation with a handwritten signature acknowledging that their electronic signature is a legally binding equivalent to their handwritten signature.

18.7 Reports to Institutional Review Board

The investigator should provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements or Institution procedures.

18.8 Quality Assurance Audits

Representatives from the CRO and/or the Sponsor or a third party selected by the Sponsor may conduct a quality assurance (QA) audit of this study. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other national health or regulatory authorities, the investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The investigator must notify the CRO in the event of a FDA or other national health authority site audit.

18.9 Records Retention

The investigator must maintain all study records (including test article disposition, informed consents/assents, CRFs and data clarification forms, if paper CRFs, source documents, correspondence, regulatory documents, contracts, etc.) for the maximum period required by the CRO or the institution where the study is conducted, whichever is longer. The Study Medication Accountability Logs will be collected at the end of the study and kept with the study records at the sites.

The investigator must contact the CRO or the Sponsor prior to destroying any records associated with this study.

If the investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to the CRO.

18.10 Record Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject or the subject's parent/guardian (if appropriate), except as necessary for monitoring by the CRO or the Sponsor, the FDA or other national health or regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study shall not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose

of the study. Prior written agreement from the CRO or the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

19. REFERENCES

1. 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.

APPENDIX 1 SAMPLE SUBJECT INSTRUCTION SHEET

A sample Subject Instruction Sheet is provided on the next page. The investigator should provide a copy of the Subject Instruction Sheet to each subject and the subject's parent/guardian at Visit 4-LTF prior to dispensing the containers of the test article(s).

SAMPLE SUBJECT AND PARENT/GUARDIAN INSTRUCTION SHEET

Please follow these instructions carefully. If you do not understand anything in these instructions, ask your parent or guardian for help. Contact/ask your parent or guardian to contact the study staff at the telephone number noted below if you have any questions:
Contact:_____ At:_____

THE AREA(S) TO BE TREATED ARE (CIRCLE ALL THAT APPLY): **FACE** **TRUNK**

STUDY MEDICATION APPLICATION:

- You will be instructed how to apply the cream in the clinic.
- You should apply the cream **TWICE DAILY to your face and/or trunk as directed by the study doctor: once in the morning and once in the evening daily with approximately eight (8) hours or more between applications.**
- Wash the area to be treated with mild soap and water; gently dry.
- Wash your hands before and after applying the cream.
- For your FACE:
  - Dispense about 1 gram of cream onto one of your fingertips and then begin to apply the cream to your entire face by dabbing small amounts gently on to multiple facial regions (forehead, cheeks, nose, and chin).
  - Spread the cream evenly with your fingertip to cover your entire face with a very thin even coat of the cream as directed by the study staff.
- For your TRUNK (optional, to be determined by you and the investigator):
  - To cover each 8.5 x 11 inch (~22 x 28 cm) area dispense about 1 gram of cream onto one of your fingertips and then begin to apply the cream to the designated areas of your trunk (shoulders, chest, and back) with acne (as needed) by dabbing small amounts over multiple regions of the area affected with acne.
  - Spread the cream evenly with your fingertip to apply a very thin even coat of the cream over the designated truncal region as directed by the study staff.
- Record date and time of cream application (and areas that were treated) in your subject diary for the face and/or trunk.
- Do not wash the treated area(s) for at least four (4) hours after application or cover or wrap areas where the cream was applied.
- Continue use of the cream as directed by the study doctor.
- If you think your acne has cleared, **DO NOT STOP APPLYING THE CREAM**. Continue to apply the cream and contact the study doctor to be seen in the clinic.

BEFORE EACH STUDY VISIT: Do not apply the cream within 4 hours of your study visit.

ADDITIONAL REMINDERS:

- Store the study medications according to the instructions on the label.
- Bring this sheet, the Subject Diary, and ALL your containers (used and unused) of study medication with you to every study visit.
- Do not allow anyone else to use the study medications and keep the containers of study medication away from children/pets.
- Discontinue use if skin irritation or rash develop and contact the study site.

STUDY VISIT SCHEDULE:

VISIT 5: Date:	Time:	VISIT 6: Date:	Time:
VISIT 8: Date:	Time:	VISIT 10: Date:	Time:

APPENDIX 2 SAMPLE SUBJECT DIARY

A copy of the Subject Diary will be provided to each study site. The investigator should provide a copy of the Subject Diary to each subject and parent/guardian (if applicable) at Visit 4-LTF (Day 1, Baseline) and all follow-up visits, as necessary.

SAMPLE SUBJECT DIARY FOR PROTOCOL CB-03-01/27

Apply the study medication as prescribed. After dosing, record the date and time. If you miss a dose, write MISSED in the space for time. Return this diary AND all tubes of cream (used and unused) at EVERY VISIT. ***ASK YOUR PARENT/GUARDIAN FOR HELP.***

If you have any questions, call NAME: ______________________________ AT: __________________________________

Date (dd-MMM-yy)	Time of Dose (HH:MM)		Areas Treated	Date (dd-MMM-yy)	Time of Dose (HH:MM)		Areas Treated
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk
___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk	___/_____/___	____:____ AM	____:____ PM	☐ Face ☐ Trunk

Site Use Only:	Diary Dispensed at: ☐ Visit 4-LTF ☐ Visit 5 ☐ Visit 6 ☐ Visit 8 ☐ Visit 10 ☐ Unscheduled	Date Dispensed: ____________________ Date Returned: ____________________

APPENDIX 3 TEST ARTICLE INFORMATION

A 3.1 Test Article Packaging and Labeling

The test articles will be packaged and labeled by the Sponsor or designee. CB-03-01 cream, 1% will be packaged in blind-end epoxy lined aluminum tubes, with a polypropylene cap closure, containing 30 grams or 60 grams of the test article. Each subject will be assigned a subject number (carried over from Phase 3 pivotal study [CB-03-01/25 or CB-03-01/26]) and provided with sufficient test article in standard packaging for the designated treatment period during the study.

Tube Labels
Each tube will contain, at a minimum, the following information: the study/protocol number, subject identifiers (e.g., subject number [to be filled in]), the contents, the tube number (to be filled in) with test article batch number), an investigational test article disclaimer (e.g., Caution: New Drug Limited by United States law to investigational use), and the appropriate storage conditions for the test article.

A 3.2 Test Article Storage and Preparation

The test articles will be stored under secure conditions until they are dispensed to the subjects. Test articles should be stored in accordance with the tube labels.

A 3.3 Dispensing Test Article

The test article must be dispensed only to study subjects and only at study sites specified on the form FDA 1572 (or other documents required by the governing national health authority) by authorized personnel as required by applicable regulations and guidelines.

Sufficient test article will be provided to each subject as needed for the designated treatment period. For those subjects with clear facial acne and no truncal acne at Baseline (Visit 4-LTF), the test article will NOT be dispensed and the subject will be reassessed at Visit 5 or earlier (after an unscheduled visit), if acne worsens (be it on the face and/or the trunk) before Visit 5.

As test article is dispensed and collected at clinic visits, tubes will be weighed to the nearest tenth gram (0.1 gram) and information should be recorded on the Study Medication Accountability Log. If treatment is discontinued on the face and trunk, all containers of the test article should be collected. If treatment is re-instated, sufficient test article will be dispensed to the subject; previously returned test article should NOT be re-dispensed, rather new containers of the test article will be dispensed as needed to the subject. Every effort to obtain the return of all dispensed tubes of the test article should be made. If these efforts fail, the reason should be recorded on the drug accountability CRF and a detailed note of the reason for failure should be made in the source documents.

A 3.4 Test Article Supply Records at Study Sites

It is the responsibility of the investigator to ensure that a current record of test article disposition is maintained. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received placed in storage area.
- Amount currently in storage area.
- Label ID number (tube numbers).
- Dates and initials of the person responsible for each product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor or third party, if applicable.
- Amount destroyed at study site, if applicable.

The CRO will provide forms to facilitate inventory control if the staff at the study site does not have an established system that meets these requirements.

A 3.5 Dose Modifications

The subject should not modify the treatment regimen without consultation with the investigator. If the subject feels that his/her acne has cleared, he/she should continue to apply the test article to the designated treatment area (face and/or trunk) as instructed by the investigator and call the investigator for an unscheduled visit. The subject should NOT change his/her dosing regimen until the investigator has documented acne improvement or worsening to support a change in the treatment recommendations.

Treatment on the face and/or trunk may be discontinued if/when acne clears (achieves an IGA of grade 0 or "minimal" grade 1) and re-instated if/when acne worsens (IGA≥2) according to the assessment of the investigator for each respective treatment area.

If skin irritation or rash develops, subject should discontinue use and contact the study site. In the event that the investigator believes dose modification is necessary due to tolerability issues (e.g., problems with tolerance), the subject's care should be discussed with the Medical Monitor prior to making any dose modifications. All dose modifications must be reported on the appropriate CRF.

A 3.6 Documentation of Application and Compliance

A Subject Diary will be dispensed to the subject to record the dates and times of all application doses and any missed doses of the test article (Appendix 2). Subjects will be

instructed to bring the diary with them to each study visit. The date and time of the first and last application of the test article will be recorded on the appropriate CRF.

A 3.7 Return and Destruction of Test Article Supplies

Upon completion or termination of the study, all test article tubes must be accounted for and any missing tubes of the test article must be explained on the completed Study Medication Accountability Log. All returned tubes will be weighed to the nearest tenth gram (0.1 gram) in order to document extent of subject exposure. Unless instructed otherwise by the Sponsor, the study site will keep the original Study Medication Accountability Log in the study file. A copy of the Study Medication Accountability Log will be returned to the Sponsor. All tubes of test article will then either be a) returned to the study Sponsor or b) emptied and provided to a sponsor-identified third party vendor for appropriate destruction, according to applicable regulations with the provision of a certificate of destruction.