A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CORTEXOLONE 17α-PROPIONATE (CB-03-01) 1% CREAM APPLIED TWICE-DAILY FOR 12 WEEKS IN SUBJECTS WITH FACIAL ACNE VULGARIS

SPONSOR PROTOCOL NUMBER: CB-03-01/26

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PROTOCOL APPROVAL

The following individuals approve version 1.0 of the CB-03-01/26 protocol dated June 11, 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: 18 Jun 2015

Date: 18JUN2015

Date: 18 Jun 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-03-01/26 Site number: ____

Version: 1.0

Date of final version: June 11, 2015

PROTOCOL SYNOPSIS

Title	A Phase 3, Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Cortexolone 17α-Propionate (CB-03-01) 1% Cream Applied Twice-Daily for 12 Weeks in Subjects with Facial Acne Vulgaris
Study Type	Phase 3
Test Articles	1. CB-03-01 (cortexolone 17α-propionate) cream, 1% 2. Vehicle cream
Study Objective	The primary objective of this study is to determine the safety and efficacy of CB-03-01 cream, 1%, versus the vehicle cream applied twice daily for 12 weeks in subjects with facial acne vulgaris.
Study Design	Multicenter, randomized, double-blind, vehicle-controlled, parallel group comparison study. A separate open-label long-term extension study is planned. Subjects completing the treatment-phase of this trial will be offered the opportunity to participate in this follow-on study (CB-03-01/27: An Open-Label, Long-Term Extension Study to Evaluate the Safety of Cortexolone 17α-Propionate (CB-03-01) Cream, 1% Applied Twice Daily for up to 12 Months in Subjects with Facial Acne Vulgaris). In this open label study, all subjects will apply the active medication (cortexolone 17α-propionate cream, 1%) twice daily for up to 9 additional months of treatment (for a total of up to 12 months; 0 or 3 months in the pivotal Phase 3 trial and an additional 9 months in the open-label long-term extension study).
Treatment Groups	Eligible subjects will be randomized (1:1) to one of two treatment groups: (1) CB-03-01 cream, 1% or (2) vehicle cream. All subjects (with supervision from parent/guardian, if needed) will apply the assigned test article twice-daily to the entire face for 12 weeks.
Duration of Treatment	12 weeks
Duration of Study	12 weeks
Study Population	Male and female subjects 9 years or older with facial acne vulgaris (Grade 3 or 4 on Investigator's Global Assessment [IGA]).
Total Number of Subjects	At least 700 subjects; 350 subjects per treatment group.
Number of Sites	Approximately 40 sites will participate in this study.

Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Subject is male or non-pregnant female, 9 years of age or older. Females must be post-menopausal[1], surgically sterile[2], or using highly effective birth control methods.[3,4] WOCBP must have a negative urine pregnancy test (UPT) at the Screening/Baseline Visit. 2. Subject has provided written and verbal 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. 3. Subject has an Investigator's Global Assessment (IGA) score of 3 or 4 [0 (clear) to 4 (severe) scale]. 4. Subject has facial acne vulgaris, which can include the nose, with at least 30 to a maximum of 75 inflammatory lesions (papules, pustules, and nodules) and 30 to a maximum of 100 non-inflammatory lesions (open and closed comedones). 5. Subject and parent/guardian (if applicable) are willing to comply with study instructions and return to the clinic for required visits. 6. Subject has used the same type and brand of make-up, other facial products (exclusive of RX/OTC acne cleansers) and hair products (e.g., shampoo, gel, hair spray, mousse, etc.) for at least one (1) month prior to the Baseline Visit and agrees to continue his/her other general skin and hair care products and regimen for the entire study.
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 evaluation of the test products or requires the use of interfering topical or systemic therapy. 3. Subject has greater than two (2) facial nodules. 4. Subject has nodulocystic acne. 5. Subject has any condition which, in the investigator's opinion, would make

[1] Defined as amenorrhea greater than 12 consecutive months.

[2] Hysterectomy, bilateral tubal ligation (at least six (6) 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, c) intrauterine device (IUD), d) partner vasectomy (performed at least six (6) 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] Women of childbearing potential (WOCBP) taking hormonal therapy for any reason exclusive for the treatment of acne (e.g., as contraception, etc.) must be on the same treatment for at least 12 weeks prior to study entry and must not change their dosing regimen during the study. Those who have used hormonal therapy prior to study entry must have discontinued use at least eight (8) weeks prior to the start of the study.

	it unsafe for the subject to participate in this research study. 6. Subject is currently enrolled in an investigational drug or device study. 7. Subject has received an investigational drug or has been treated with an investigational device within 30 days prior to the initiation of treatment (Baseline). 8. Subject has facial hair that could interfere with the study assessments in the opinion of the investigator. 9. Subject and parent/guardian (if applicable) are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function. 10. 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. 11. Subject has known hypersensitivity or previous allergic reaction to any of the active or inactive components of the test articles (see Section 6.1). 12. Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the trial. 13. Subject has used any of the following topical anti-acne preparations or procedures on the face: • Topical anti-acne treatments including, but not limited to, over-the-counter (OTC) acne cleansers or treatments, benzoyl peroxide, antibiotics, azelaic acid, sulfa based products, corticosteroids and salicylic acid within two (2) weeks of the initiation of treatment. • Retinoids, including tazarotene, adapalene, tretinoin, within four (4) weeks of the initiation of treatment. • Light treatments, microdermabrasion, or chemical peels within eight (8) weeks of the initiation of treatment. 14. Subject has used the following systemic anti-acne medications: • Corticosteroids (including intramuscular and intralesional injections) within four (4) weeks of the initiation of treatment. Inhaled, intranasal, or ocular corticosteroids are allowed if use is stable (stable use is defined as dose and frequency unchanged for at least four (4) weeks prior to the initiation of treatment). • Antibiotics within four (4) weeks of the initiation of treatment with the exception of five (5) days or less of antibiotic therapy during this period, BUT with no antibiotics use permitted within one (1) week prior to the initiation of treatment. • Spironolactone within eight (8) weeks of the initiation of treatment with the exception of five (5) days or less of spironolactone therapy during this period, BUT with no spironolactone use permitted within one (1) week prior to the initiation of treatment. • Retinoid therapy within six (6) months of the initiation of treatment. • Other systemic therapy which may materially affect the subject's acne in the opinion of the investigator.
Study Procedures	The study will consist of a Screening/Baseline Visit and three (3) scheduled visits. 1. Visit 1 (Screening/Baseline): At Visit 1, 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, consenting subjects will have their medical and dermatological history, dermatologic exam,

	and inclusion/exclusion criteria reviewed to determine subject eligibility. Subjects that require a "washout" period prior to enrollment to meet inclusion/exclusion criteria requirements will be required to return to the clinic within 45 days to complete the remaining activities. Subjects who require "washout" for longer than 45 days will be re-consented. A brief physical examination including vital signs, UPT (if applicable), electrocardiogram (ECG), Fitzpatrick Skin Type assessment, clinical evaluations (lesions counts, IGA, as well as baseline local skin reactions (LSRs) pre-application), and photographs will be performed at this visit. Prior and concomitant therapy and concomitant medications/procedures will be reviewed. Subjects will be randomized and assigned a test article kit number. Test article and Subject Diary will be dispensed. Subjects and parent/guardian (if applicable) will be instructed on how to apply the test article and to record applications in the Subject Diary. The first dose will be applied during this visit under supervision of the investigator. Adverse events (AEs) and LSRs post-application will be assessed. The subject will be scheduled for the first follow-up visit. 2. Visits 2 and 3 (Weeks 4 & 8): Subjects will return after the initial treatment for clinical evaluations (lesion counts, IGA, AEs, and LSRs), UPT (if applicable), and review of concomitant medications/procedures. Test article application and compliance will be reviewed (from Subject Diary), test article and Subject Diary will be dispensed/returned (as required), and photography will be performed. The subject will be scheduled for the next follow-up visit. 3. Visit 4 (Final Visit, Week 12 & Early Termination): Subjects will return for the final visit for review of concomitant medications/procedures, UPT (if applicable), ECG, clinical evaluations (lesion counts, IGA, AEs, and LSRs), and photography. All test article will be returned and compliance documented (from Subject Diary).
Study Measurements	***Efficacy*** will be assessed by the investigator as follows: • Investigator's Global Assessment (IGA): Overall severity of acne using a five-point scale from 0 = clear to 4 = severe will be conducted at each visit. This is a static morphological scale that refers to a point in time and not a comparison to Baseline. • Acne Lesion Counts: Total lesions, including inflammatory lesions (papules, pustules, and nodules) and non-inflammatory lesions (open and closed comedones), on the face will be accurately counted, but recorded separately at each visit. Assessment of subject satisfaction with the treatment will be obtained using a four-point scale from 1=excellent (very satisfied) to 4=poor (not satisfied at all) at the final visit (Week 12). ***Safety*** will be assessed by the investigator via the evaluation of local and systemic AEs and UPTs at each visit (Baseline, Weeks 4, 8, and 12, or at the end of treatment). ECGs will also be assessed at Baseline and Week 12. LSRs including telangiectasia, skin atrophy, striae rubrae, erythema, edema, and scaling/dryness will be assessed by the investigator at each visit using a

	five-point ordinal scale (0 = none, 1 = trace, 2 = mild, 3 = moderate, and 4 = severe). Subjects will be asked to rate the severity of stinging/burning and pruritus using a four-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) at each visit (Baseline [pre- and post-application], and Weeks 4, 8, and 12).
Study Endpoints	**Efficacy Endpoints:** *Primary Endpoints (Hierarchical)* • **P1:** Proportion of subjects in each treatment group achieving "success" at Week 12, with "success" defined as an IGA score of "clear (score=0)" or "almost clear (score=1)" AND at least a two-point reduction in IGA compared to Baseline. • **P2:** Absolute change from Baseline in non-inflammatory lesion counts in each treatment group at Week 12. • **P3:** Absolute change from Baseline in inflammatory lesion counts in each treatment group at Week 12. *Secondary Endpoints (Hierarchical)* • **S1:** Absolute change from Baseline in total lesions counts in each treatment group at Week 12. • **S2:** Percent change from Baseline in total lesions counts in each treatment group at Week 12. • **S3:** Percent change from Baseline in non-inflammatory lesions count in each treatment group at Week 12. • **S4:** Percent change from Baseline in inflammatory lesions count in each treatment group at Week 12. **Safety Endpoints:** • Local and systemic AEs at every visit (Baseline, Weeks 4, 8, and 12). • LSRs: telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus scored by frequency and severity at every visit (Baseline, Weeks 4, 8, and 12). • UPTs in all WOCBP at every visit (Baseline, Weeks 4, 8, and 12). • Material changes from Baseline in ECGs at Week 12.
Sample Size Calculations and Power Considerations	Assumptions used for sample size calculations were estimated from Phase 2 Dose Escalation Study (171-7151-201), using a subset of subjects with 30-75 inflammatory lesions and 30-100 non-inflammatory lesions at Baseline. All the hypothesis tests for the primary endpoints have to be performed at the same significance level α=0.05 two-sided and the failure to reject a null hypothesis will imply the failure of rejecting all of the subsequent null hypotheses. In order to keep the overall Type II error β=0.1 for the whole study, the sample size for the three hypothesis tests on the primary endpoints will be calculated considering an individual Type II error β=0.033. For an IGA success rate of (continuity corrected) 14.00% for CB-03-01 cream and 2.17% for vehicle cream (odds ratio=7.3), sample size was estimated to be 202 subjects per treatment group.

	For a mean absolute change from Baseline in non-inflammatory lesion counts of -22 for CB-03-01 cream and -1 for vehicle cream (standard deviation=17), sample size was calculated to be 19 subjects per treatment group. For a mean absolute change from Baseline in inflammatory lesion counts of -15 for CB-03-01 cream and -10 for vehicle cream (standard deviation=17), sample size was calculated to be 334 subjects per treatment group. The hypothesis test for the secondary endpoints will be performed at the same significance level α=0.05 two-sided of the primary endpoints if and only if all the null hypotheses on the primary endpoints are rejected. For a mean absolute change from Baseline in total lesion counts of -35 for CB-03-01 cream and -13 for vehicle cream (standard deviation=17), sample size was calculated to be 13 subjects per treatment group. For a mean percent change from Baseline in total lesion counts of -35 for CB-03-01 cream and -14 for vehicle cream (standard deviation=40), sample size was calculated to be 77 subjects per treatment group. For a mean percent change from Baseline in non-inflammatory lesion counts of -33 for CB-03-01 cream and -5 for vehicle cream (standard deviation=40), sample size was calculated to be 43 subjects per treatment group. For a mean percent change from Baseline in inflammatory lesion counts of -37 for CB-03-01 cream and -23 for vehicle cream (standard deviation=40), sample size was calculated to be 172 subjects per treatment group. Based on those assumptions, at least 350 subjects in each treatment group (CB-03-01 cream, 1% BID and vehicle BID) will be included into each Phase 3 study to provide sufficient power (90%) with the chosen primary endpoints.
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. Summaries will be provided for each treatment group. **Study Sets:** 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 randomized 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, with the ITT set considered as the primary set for statistical analysis. Multiple imputation will be used to impute missing values for the primary endpoints and absolute change in total lesions count (S1) in the ITT analyses. Sensitivity

	analyses will be performed to investigate the robustness of the results obtained on the ITT set for the primary endpoints (change from Baseline in non-inflammatory and inflammatory lesion counts and IGA "success" at Week 12). Missing values for the other secondary endpoints (i.e., S2-S4: percent change in lesions counts) will be calculated using the values obtained from the multiple imputation of the primary efficacy endpoints and secondary efficacy endpoint #1 (S1). **Efficacy Analyses:** *Primary Efficacy Analysis* Hypothesis tests on the primary endpoints will be conducted in hierarchical order for P1 through P3. **P1:** A logistic regression model with treatment and analysis center as fixed effects will be used to compare the proportion of subjects achieving "success" in each treatment group at Week 12, where "success" is defined as an IGA score of "clear (score=0)" or "almost clear (score=1)" AND at least a two-point improvement in IGA compared to Baseline. **P2:** An analysis of covariance (ANCOVA) will be used to compare the absolute change from Baseline in non-inflammatory lesion counts in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline non-inflammatory lesion count as the covariate. **P3:** An ANCOVA will be used to compare the absolute change from Baseline in inflammatory lesion counts in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline inflammatory lesion count as the covariate. *Secondary Efficacy Analysis* Hypothesis tests on the secondary endpoints will be conducted in hierarchical order for S1 through S4. **S1:** An ANCOVA will be used to compare the absolute change from Baseline in total lesion counts in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline total lesion count as the covariate. **S2:** An ANCOVA will be used to compare the percent change from Baseline in total lesion counts in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline total lesion count as the covariate. **S3:** An ANCOVA will be used to compare the percent change from Baseline in non-inflammatory lesion counts in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline non-inflammatory lesion count as the covariate. **S4:** An ANCOVA will be used to compare the percent change from Baseline in inflammatory lesion counts in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline inflammatory lesion count as the covariate.

Treatment Compliance and Extent of Exposure Analyses:

Treatment Compliance

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

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

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

Descriptive statistics will be used to summarize test article compliance at each visit and overall for the ITT and PP sets. The proportion of compliant and non-compliant subjects will be summarized by table of frequencies at each visit and overall for the ITT and PP sets. Subjects with an overall compliance not evaluable (due to missing data) or less than 80% will be excluded from the PP set.

Extent of Exposure

Descriptive statistics will be used to summarize exposure to test article for the ITT, PP, and Safety 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.

Safety Analyses:

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 by treatment group and severity at each visit.

Adverse Events (AEs)

Pre-treatment AEs (PTAEs) and Treatment Emergent AEs (TEAEs) will be coded using the MedDRA coding dictionary. TEAEs will be summarized by treatment group and overall. The number and proportion of subjects with any TEAE and the number of TEAEs will be tabulated by MedDRA system organ class (SOC) and preferred term (PT), seriousness, relationship to test article, and severity.

Electrocardiograms (ECGs)

ECGs will be evaluated for any material change during the study period. Results (normal/borderline/abnormal) of the ECG and descriptive statistics will be provided by treatment group at each visit for heart rate, RR duration, PR duration, QRS duration, QT duration including Bazett's and Fridericia's corrections, and P axis for the Safety set. Changes in overall interpretation (normal/abnormal/borderline) of the ECG from Baseline to Week 12 will be examined using shift tables.

SCHEDULE OF EVENTS

PROCEDURES	Visit 1 Screening/ Baseline Day 1	Visit 2 Week 4 (Day 29 ± 5)	Visit 3 Week 8 (Day 57 ± 7)	Visit 4 Week 12[1] (Day 85 ± 10)
Informed Consent/Assent[2]	X[2]			
Medical/Dermatological History	X			
Demographics	X			
Inclusion/Exclusion Criteria	X			
Dermatologic & Limited Physical Exam	X			
Fitzpatrick Skin Type Assessment	X			
Urine Pregnancy Tests[3]	X	X	X	X
Electrocardiograms	X			X
Photographs	X	X	X	X
Lesion Counts	X	X	X	X
Investigator's Global Assessment	X	X	X	X
Local Skin Reaction Assessment	X (pre- & post-application)	X	X	X
Review of Concomitant Medications & Procedures	X	X	X	X
Study Medication and Diary Dispensed & Collected[4,5]	X	X	X	X
Review of Compliance		X	X	X
Adverse Events Evaluation	X	X	X	X

1. Subjects who terminate early shall complete all final visit activities designated at Week 12.
2. Consent/assent may be performed up to 45 days prior to the Baseline Visit. Subjects who require "washout" for longer than 45 days will be re-consented.
3. Testing to be conducted on all WOCBP (see Section 5.1.1 for definition). UPT minimal sensitivity is 25 mIU/mL.
4. Instruct subject and the subject's parent/guardian on test article application and provide instruction sheet after assessing the subject's use of the test article with respect to the amount and number of doses applied since the last visit.
5. Dispense Subject Diary at initial and subsequent visits, as needed.

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BID	Twice a day
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
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HPA	Hypothalamic-Pituitary-Adrenal
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-Counter
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
QA	Quality Assurance
QD	Once a day
RX	Prescription
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UPT	Urine Pregnancy Test
WOCBP	Women of Childbearing Potential

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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].

In single-dose studies in mouse and in rat, and following repeated subcutaneous administration in rats, and dermal administration in rabbits and minipigs, the drug was well tolerated with no significant local or unexpected systemic effects. CB-03-01 is not mutagenic in the Ames test or in the human chromosome aberration test, and it is not a skin sensitizer.

To date, four Phase 1 and three Phase 2 clinical studies have been completed with CB-03-01 cream in Europe and the United States, with over 500 subjects exposed to CB-03-01 creams. All studies were conducted using CB-03-01 cream, 1%; additional concentrations of CB-03-01 cream (0.1% and 0.5%) were also used in the most-recent Phase 2 Dose-Escalating study. The studies included:

1. A Phase 1 Single Dose Pharmacokinetics (PK) Study in 24 healthy volunteers [randomized, double-blind, vehicle-controlled, single-ascending dose],
2. A Phase 1 Repeat Dose PK Study in 24 healthy volunteers [randomized, vehicle-controlled, 14-day repeat-dose],
3. A Phase 1 Steady State PK Study in 8 subjects with acne vulgaris [single center, open-label, pilot, 6-week repeat-dose]
4. A Phase 1 Three-week Cumulative Skin Irritation Study in 36 healthy volunteers,
5. A Phase 2 Hypothalamic-Pituitary-Adrenal axis (HPA)/PK study in 42 subjects with acne vulgaris [open-label, 14-day repeat-dose]
6. A Phase 2 Comparator Proof of Concept Study in 72 adult subjects with facial acne vulgaris [randomized, double-blind, vehicle-controlled, active-comparator (Retin-A® [tretinoin] 0.05% cream), 8-week repeat-dose], and
7. A Phase 2 Dose-Escalating Study in 363 subjects with facial acne vulgaris [multi-center, randomized, double-blind, vehicle controlled, 12-week repeat-dose]

Overall, the data that resulted from the completion of the aforementioned studies has demonstrated that CB-03-01 creams selected for clinical development (a) are well tolerated locally, (b) result in minimal systemic exposure when applied topically, (c) have a clinical safety profile without any concern and similar to the placebo, and (d) at 1%

concentration applied BID are significantly more effective than its vehicle at reducing inflammatory and non-inflammatory lesions counts in adolescent and adult subjects.

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

The concentration of CB-03-01 selected for the initial clinical studies (1%) was based on antiandrogenic activity in the hamster flank organ test in which the best effective concentration was 0.8% [1]. The results of the Phase 2 Dose Escalation Study demonstrated that CB-03-01 cream, 1% applied BID had more favorable results than other treatments (0.1% BID, 0.5% BID, and 1% QD) and no material safety issues were noted with any of the concentrations of CB-03-01 cream [2]. Based on the collective findings of the previous Phase 1 and Phase 2 studies, CB-03-01 cream, 1% BID appears to be the best treatment candidate to advance for further clinical study and development as a topical treatment for acne vulgaris. Thus, the present Phase 3 study has been designed to determine and compare the efficacy of treatment with CB-03-01 cream, 1% and the vehicle cream applied twice daily for 12 weeks in subjects with moderate to severe facial acne vulgaris.

3. OBJECTIVE

The primary objective of this study is to determine the safety and efficacy of CB-03-01 cream, 1% versus the vehicle cream applied twice daily for 12 weeks in subjects with facial acne vulgaris.

4. STUDY DESIGN

This is a multicenter, randomized, double-blind, vehicle-controlled, parallel-group comparison study of safety and efficacy for CB-03-01 cream, 1% in male and female subjects, 9 years or older with moderate to severe acne vulgaris on the face. Eligible subjects must have acne vulgaris of the face (which can include the nose) with an Investigator's Global Assessment (IGA) score of 3 or 4, at least 30 to a maximum of 75 inflammatory lesions (papules, pustules, and nodules), and at least 30 to a maximum of 100 non-inflammatory lesions (open and closed comedones). At least 700 subjects will be enrolled at approximately 40 sites. Subjects will be randomized in a 1:1 ratio to one of two treatment groups:

1. CB-03-01 (cortexolone 17α-propionate) cream, 1%
2. Vehicle cream

All subjects will apply the assigned test article to the face twice daily for 12 weeks (see Section 6).

In addition, a separate open-label long-term extension study is planned. Subjects completing the treatment-phase of this trial will be offered the opportunity to participate in this follow-on study (CB-03-01/27: An Open-Label, Long-Term Extension Study to Evaluate the Safety of Cortexolone 17α-Propionate (CB-03-01) Cream, 1% Applied Twice Daily for up to 12 Months in Subjects with Facial Acne Vulgaris). In this open label study, all subjects will apply the active medication (cortexolone 17α-propionate cream, 1%) twice daily for up to 9 additional months of treatment (for a total of up to 12 months; 0 or 3 months in the pivotal Phase 3 trial and an additional 9 months in the open-label long-term extension study).

5. STUDY POPULATION

5.1 Subject Eligibility

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

5.1.1 Inclusion Criteria

1. Subject is male or non-pregnant female, 9 years of age or older. Females must be post-menopausal[5], surgically sterile[6], or using highly effective birth control methods.[7,8] WOCBP must have a negative urine pregnancy test (UPT) at the Screening/Baseline Visit.
2. 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

[5] Defined as amenorrhea greater than 12 consecutive months.
[6] Hysterectomy, bilateral tubal ligation (at least six (6) months prior to study entry), or bilateral oophorectomy.
[7] Highly effective contraception includes a) total abstinence, b) oral, injected, or implanted hormonal methods of contraception, c) intrauterine device (IUD), d) partner vasectomy (performed at least six (6) 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].
[8] Women of childbearing potential (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 [defined as amenorrhea >12 consecutive months]. WOCBP taking hormonal therapy for any reason exclusive of the treatment for acne (e.g., as contraception, etc.) must be on the same treatment for at least 12 weeks prior to study entry and must not change their dosing regimen during the study. Those who have used hormonal therapy prior to study entry must have discontinued use at least eight (8) weeks prior to the start of the study.

the study the subject must provide written informed consent at that time to continue study participation.
3. Subject has an Investigator's Global Assessment (IGA) score of 3 or 4 [0 (clear) to 4 (severe) scale].
4. Subject has facial acne vulgaris, (which can include the nose), with at least 30 to a maximum of 75 inflammatory lesions (papules, pustules, and nodules) and 30 to a maximum of 100 non-inflammatory lesions (open and closed comedones).
5. Subject and parent/guardian (if applicable) are willing to comply with study instructions and return to the clinic for required visits.
6. Subject has used the same type and brand of make-up, other facial products (exclusive of RX/OTC acne cleansers) and hair products (e.g., shampoo, gel, hair spray, mousse, etc.) for at least one (1) month prior to the Baseline Visit and agrees to continue his/her other general skin and hair care products and regimen for the entire study.

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 evaluation of the test products or requires the use of interfering topical or systemic therapy.
3. Subject has greater than two (2) facial nodules.
4. Subject has nodulocystic acne.
5. Subject has any condition which, in the investigator's opinion, would make it unsafe for the subject to participate in this research study.
6. Subject is currently enrolled in an investigational drug or device study.
7. Subject has received an investigational drug or has been treated with an investigational device within 30 days prior to the initiation of treatment (Baseline).
8. Subject has facial hair that could interfere with the study assessments in the opinion of the investigator.
9. Subject and parent/guardian (if applicable) are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
10. 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.
11. Subject has known hypersensitivity or previous allergic reaction to any of the active or inactive components of the test articles (see Section 6.1).
12. Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the trial.
13. Subject has used any of the following topical anti-acne preparations or procedures on the face:
    - Topical anti-acne treatments including, but not limited to, over-the-counter (OTC) acne cleansers or treatments, benzoyl peroxide, antibiotics, azelaic acid, sulfa

based products, corticosteroids and salicylic acid within two (2) weeks of the initiation of treatment.
- Retinoids, including tazarotene, adapalene, tretinoin, within four (4) weeks of the initiation of treatment.
- Light treatments, microdermabrasion, or chemical peels within eight (8) weeks of the initiation of treatment.

14. Subject has used the following systemic anti-acne medications:
- Corticosteroids (including intramuscular and intralesional injections) within four (4) weeks of the initiation of treatment. Inhaled, intranasal or ocular corticosteroids are allowed if use is stable (stable use is defined as dose and frequency unchanged for at least four (4) weeks prior to the initiation of treatment).
- Antibiotics within four (4) weeks of the initiation of treatment with the exception of five (5) days or less of antibiotic therapy during this period, BUT with no antibiotics use permitted within one (1) week prior to the initiation of treatment.
- Spironolactone within eight (8) weeks of the initiation of treatment with the exception of five (5) days or less of spironolactone therapy during this period, BUT with no spironolactone use permitted within one (1) week prior to the initiation of treatment.
- Retinoid therapy within six (6) months of the initiation of treatment.
- Other systemic therapy which may materially affect the subject's acne in the opinion of the investigator.

5.1.3 Subject Withdrawal Criteria

Procedures for handling subjects who are discontinued from the study are described in Section 13.2. Subjects who are discontinued will not be replaced.

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.
Placebo name:	Vehicle Cream
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

At the first visit, the subjects will be instructed to wash their entire face (the area to be treated) 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 cream, how much of the test article to use, and where to apply the assigned test article. The first application of cream should be applied in the office at Visit 1 under supervision of the study staff after subject has been deemed eligible. Typically, about 1 gram of the cream will be dispensed onto a fingertip and applied to the face by dabbing small amounts gently on multiple regions of the face (e.g., forehead, nose, cheeks, chin). Using a fingertip, the cream will be spread to provide a thin, uniform layer of the cream **over the entire face**.

Subjects and parents/guardians (if applicable) will be instructed to apply the cream to the whole face twice daily (morning and in the evening) for 12 weeks. The subject should ideally allow at least eight (8) hours between applications. All subjects should not wash the treated area for at least four (4) hours following test article application; and **MUST NOT APPLY THE TEST ARTICLE WITHIN FOUR (4) HOURS PRIOR TO ANY STUDY VISIT.**

Subjects will be provided with a Subject Diary to record the dates and time of application. Subjects will be instructed to only apply the study cream to the face 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 also be provided with a Subject Instruction Sheet providing them with instructions on how to use and store the cream at home during the study period.

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).

Subjects who are not compliant with applying the creams 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

These test articles are 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 articles 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

Subjects who are eligible for enrollment into the study will be randomized to receive CB-03-01 cream or vehicle cream in a 1:1 ratio. The randomization scheme will be blocked by investigational site. At each site, subject kits will be dispensed according to the kit number assigned by an IVRS/IWRS system as subjects are enrolled. At each site, the study staff will add the site number (provided to each site) and the subject number (starting with 001) to each kit label. The kit number dispensed to each subject will also be recorded on the source documents and CRFs. Treatment group designation will remain blinded until the final database is locked (unless unblinding is required as described in Section 15). Subjects who withdraw prematurely from the study will not be replaced.

8. PRIOR AND CONCOMITANT THERAPIES

Current medications and any medications taken in the 30 days prior to the start of the study (Screening, Visit 1) 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 this page prior to commencing the use of the test article.

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 1 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 adverse event.

8.1 Prohibited Medications or Therapies

Medications or therapies that are prohibited during the duration of the study are as follows:

Prior to entry into the study, subjects must not use the medications and/or procedures on the face as specified in Section 5.1.2.

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

- Topical anti-acne treatments including, but not limited to, OTC acne cleansers or treatments, benzoyl peroxide, antibiotics, azelaic acid, sulfa based products, corticosteroids, and salicylic acid.
- Retinoids including tazarotene, adapalene, and tretinoin.
- Light treatments (including artificial tanning devices), microdermabrasion, or chemical peels.
- Any other investigational drug or use of any investigational device
- Systemic medications with potential anti-acne effects including:
  - Corticosteroids (including intramuscular and intralesional injections). Inhaled, intranasal, or ocular corticosteroids are allowed (see Section 8.2).
  - Antibiotics
  - Spironolactone
  - Retinoid therapy
  - The addition of hormonal contraception
  - Change to pre-existing hormonal contraception
  - Other systemic therapy, which may materially affect the subject's acne in the opinion of the investigator.

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

8.2 Allowed Medications or Therapies

Subjects must be on a consistent skin care program (make-up, moisturizers, soap, sunscreen, etc. of their choice, exclusive of RX/OTC acne cleansers) for at least one (1) month prior to enrollment. The subject's skin care regimen will be reviewed and approved prior to their randomization. This skin care program should not contain any OTC products with significant levels of anti-acne ingredients such as retinol or alpha-hydroxy acids (i.e., lactic acid, glycol acid, etc. at greater than 5%).

No additional medications, including OTC preparations, should be used without the knowledge and, if possible, permission of the investigator. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health. The addition, discontinuation, or dose change of any concomitant medications will be documented in the source documents.

Medications will be permitted, at the discretion of the investigator, to treat local skin reactions, if applicable.

Intranasal, inhaled, and ophthalmic steroids used for the management of allergies, pulmonary disorders, or other conditions exclusive of acne are NOT considered prohibited medications, but should be recorded on the Concomitant Medication Form.

WOCBP taking per protocol allowed hormonal contraception therapy at enrollment must remain on the same treatment for the duration of the trial.

Any changes in concomitant therapies during the study must be recorded on the CRFs. The reason for any changes in concomitant medications or therapies/procedures should be reported and should reflect either a baseline medical condition documented in the medical history of the CRF or an AE.

9. STUDY PROCEDURES

The study will consist of a Screening/Baseline Visit and three (3) scheduled visits.

Specific activities for each study visit are listed below.

9.1 Visit 1 (Day 1): Screening/Baseline

Subjects can be screened for the study up to 45 days before Visit 1. During screening, the study requirements will be reviewed, written informed consent/assent obtained, and eligibility confirmed. If applicable, the washout from prohibited medications or treatments will be determined and implemented. Subjects who require "washout" for longer than 45 days will be re-consented.

At Screening, 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.
- Complete review and documentation of the subject's medical and dermatological history and demographic information.
- Record any concomitant medications and therapies.
- Confirm the subject meets the inclusion/exclusion criteria.
- Have subject complete washout from any prohibited medications, if necessary.

Once the Screening procedures have been completed, the investigator or designee will:

- Perform a dermatologic exam and brief physical exam (including vital signs, height, and weight).
- Perform a Fitzpatrick Skin Type assessment (see Section 10.3).
- Perform a UPT for all WOCBP (see Section 5.1.1 for definition). The results must be negative for the subject to be enrolled into the study.
- Perform an ECG.
- Perform IGA (see Section 10.1) and acne lesion counts (see Section 10.2) prior to the first application of the test article.
- Record Baseline LSRs (prior to application of the test article) (see Section 10.4).
- Perform photography for all subjects at all sites (see Section 11).
- If the subject meets the inclusion/exclusion criteria, randomize the subject to the next available (lowest) subject number.
- Weigh and dispense initial tube(s) of test article.
- Complete the Study Medication Accountability Log.
- Dispense the Subject Instruction Sheet to the subject and parent/guardian (if applicable) (Appendix 1).
- Dispense the Subject Diary (Appendix 2) to the subject and parent/guardian (if applicable) and provide completion instructions.
- Instruct the subject and parent/guardian (if applicable) where and how to apply the initial dose of test article to the acne lesions on the face following the procedures in Section 6.2. The first application should occur in the office under supervision of the study staff.
- Record any AEs and LSRs (see Section 10.4) after the initial application of the test article.
- Instruct the subject and parent/guardian (if applicable) to apply the test article (about 1 gram) to the whole face twice per day, with at least eight (8) hours between applications.
- Update the Screening and Enrollment Log.
- Schedule Visit 2 (Week 4).

9.2 Visits 2 (Week 4) and 3 (Week 8)

The visit windows for Visits 2 and 3 are Day 29 ± 5 and Day 57 ± 7, respectively.

At these visits, the investigator or designee will:

- Observe/query the subject about any changes in his/her health since the previous study visit, including concomitant medications/therapies, and document the findings.
- Assess any LSRs associated with the subject's acne or the topical application of the test article (see Section 10.4).

- Initiate/update the appropriate AE form, if applicable.
- Perform a UPT for all WOCBP (see Section 5.1.1 for definition).
- Perform photography (see Section 11).
- Perform IGA (see Section 10.1) and acne lesion counts (see Section 10.2).
- Collect and dispense another (new) Subject Diary, if necessary (Appendix 2).
- Collect and weigh used tubes of test article and weigh/dispense additional tubes, if necessary (see Appendix 3). If subject is under or over utilizing the test article remember to re-educate them regarding proper use and application.
- Complete the Study Medication Accountability Log.
- Review subject instructions on the proper application of the test article (Appendix 1) with the subject and parent/guardian (if applicable) and the recommended amount of test article per application, as well as review and discuss any discrepancies or concerns with the subject regarding their use of the diary in addition to the amount of test article used since the last visit, if applicable. Subjects who have missed multiple applications of the test article may be discontinued from the study, at the discretion of the investigator.
- Instruct the subject and parent/guardian (if applicable) to continue application of the test article (about 1 gram) to the whole face twice per day, with at least eight (8) hours between applications.
- Schedule the next visit.

9.3 Visit 4 (Week 12): End of Study

The visit window for Visit 4 is Day 85 ± 10.

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 concomitant medications/therapies, and document the findings.
- Assess any LSRs associated with the subject's acne or the topical application of the test article (see Section 10.4).
- Initiate/update the appropriate AE form, if applicable.
- Perform a UPT for all WOCBP (see Section 5.1.1 for definition).
- Perform an ECG.
- Perform photography (see Section 11).
- Perform IGA (see Section 10.1) and acne lesion counts (see Section 10.2).
- Collect the Subject Diary (Appendix 2).
- Collect and weigh used and unused tubes of test articles (see Appendix 3).
- Complete the Study Medication Accountability Log.
- Complete End of Study Form and discharge subject from the study.

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)

At every study visit, overall severity of acne using a five-point scale from 0 = clear to 4 = severe will be conducted at each visit. This is a static morphological scale that refers to a point in time and not a comparison to Baseline. Subjects must have an IGA score of 3 (moderate) or 4 (severe) at Baseline.

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

10.2 Acne Lesion Counting

The number of inflammatory lesions (papules, pustules, and nodules) and non-inflammatory lesions (open and closed comedones) on the face vertically from the hairline to mandible rim and horizontally from ear to ear, including those on the nose will be counted to determine subject eligibility at Visit 1. Subjects must have at least 30 to a maximum of 75 inflammatory lesions and 30 to a maximum of 100 non-inflammatory lesions on the face (which can include the nose) at Baseline.

Lesions are defined as follows:

- Comedones- open (blackheads) and closed (whiteheads).
- Papules- raised inflammatory lesions with no visible purulent material.
- Pustules- raised inflammatory lesions with visible purulent material.
- Nodules- Any circumscribed, inflammatory masses greater or equal to 5 mm in diameter with or without cystic changes.

10.3 Fitzpatrick Skin Type Assessment

At Visit 1, the investigator or designee will document the subject's skin phototype (I-VI) using the Fitzpatrick Skin Type Assessment as described below:

FITZPATRICK SKIN TYPE		
Skin Phototype	**Typical Features**	**Tanning ability**
I	Pale white skin, blue/hazel eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

10.4 Local Skin Reactions (LSRs)

At every study visit, the investigator or designee will document the severity of the following LSRs known to be associated with application of topical steroids:

- 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, 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 area 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.

11. PHOTOGRAPHY

Photography documentation is required in this study. Photographs taken as part of this study will be used to document the effects of treatment, AEs, or other findings during the trial. Color photographs (both sides of the face and the front of the face) of the areas with acne lesions of all enrolled subjects will be performed at the Baseline Visit prior to application of the test articles and at Visits 2, 3, and 4. The study sites will be provided with suggested guidelines to assist them in taking standardized photographs. In addition, investigators at all study sites may take photos as they deem appropriate to document the clinical status of the subject (e.g., an AE, etc.). Photographs taken for 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 is 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 every visit on all WOCBP (see Section 5.1.1 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 12-week course of treatment as specified in this protocol 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 12-week treatment period for any reason, the Visit 4 procedures should be completed at that time. Subjects who withdraw prematurely will not be replaced. 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. During any wash out and baseline periods, any changes in the health of subjects should be recorded as changes in medical history unless the event occurred as a result of a study-related procedure and is unanticipated, in such cases, the event should be recorded as an AE and reported to the Institutional Review Board (IRB) as an "unanticipated problem" in accordance with local procedures. 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 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 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 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.** 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 Sponsor, if available.

As required, 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 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 5.1.1 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 monthly throughout the course of the study. 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 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 CRO, on the appropriate 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

Blinding is important for the integrity of this clinical drug trial. However, the blind may be broken in the event of a medical emergency in a subject, in which knowledge of the test article identity is critical to the subject's management. Before breaking the blind for a subject, the investigator should determine that the information is necessary (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not test article related, the problem may be effectively managed by assuming that the subject is receiving active product without the need for unblinding. The need to break the blind should first be discussed with the responsible Medical Monitor and the best method to do this will be determined.

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, blinding/unblinding, storage and preparation, dispensing, accountability etc. is included in Appendix 3.

16.2 Supplies Provided by CRO

- CRFs
- Source document draft templates
- Site regulatory binder or document filing system
- UPT kits
- Weighing scales (if necessary)
- High quality digital camera and any associated software (if needed)

16.3 Supplies Provided by Investigator

- Urine collection containers for UPTs
- Computer to store and view photographs of subjects

17. STATISTICAL CONSIDERATIONS

17.1 Study Endpoints

17.1.1 Efficacy Endpoints

Primary Endpoints (Hierarchical):

- **P1:** Proportion of subjects in each treatment group achieving "success" at Week 12, with "success" defined as an IGA score of "clear (score=0)" or "almost clear (score=1)" AND at least a two-point reduction in IGA compared to Baseline.
- **P2:** Absolute change from Baseline in non-inflammatory lesion counts in each treatment group at Week 12.
- **P3:** Absolute change from Baseline in inflammatory lesion counts in each treatment group at Week 12.

Secondary Endpoints (Hierarchical):

- **S1:** Absolute change from Baseline in total lesion counts (including inflammatory and non-inflammatory) in each treatment group at Week 12.
- **S2:** Percent change from Baseline in total lesion counts (including inflammatory and non-inflammatory) in each treatment group at Week 12.
- **S3:** Percent change from Baseline in non-inflammatory lesions count in each treatment group at Week 12.
- **S4:** Percent change from Baseline in inflammatory lesions count in each treatment group at Week 12.

17.1.2 Safety Endpoints

- Local and systemic AEs at every visit (Baseline, Weeks 4, 8, and 12).
- LSRs: telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus scored by frequency and severity at every visit (Baseline, Weeks 4, 8, and 12).
- UPTs in all WOCBP at every visit (Baseline, Weeks 4, 8, and 12).
- Material changes from Baseline in ECGs at Week 12.

17.2 Sample Size Calculations and Power Considerations

Assumptions used for sample size calculation were estimated from Phase 2 Dose Escalation Study (171-7151-201) [2], using a subset of subjects with 30-75 inflammatory lesions and 30-100 non-inflammatory lesions at Baseline. Sample size calculations were performed on the basis of the formulas for testing superiority in terms of mean differences and odds ratio of Wang and Chow.

All the hypothesis tests for the primary endpoints have to be performed at the same significance level $\alpha=0.05$ two-sided and the failure to reject a null hypothesis will imply the failure of rejecting all of the subsequent null hypotheses.

In order to keep the overall Type II error $\beta=0.1$ for the whole study, the sample size for the three hypothesis tests on the primary endpoints will be calculated considering an individual Type II error $\beta=0.033$.

For an IGA success rate of (continuity corrected) 14.00% for CB-03-01 cream and 2.17% for vehicle cream (odds ratio=7), sample size was estimated to be 202 subjects per treatment group.

For a mean absolute change from Baseline in non-inflammatory lesion counts of -22 for CB-03-01 cream and -1 for vehicle cream (standard deviation=17), sample size was calculated to be 19 subjects per treatment group.

For a mean absolute change from Baseline in inflammatory lesion counts of -14 for CB-03-01 cream and -11 for vehicle cream (standard deviation=17), sample size was calculated to be 334 subjects per treatment group.

The hypothesis test for the secondary endpoints will be performed at the same significance level α=0.05 two-sided of the primary endpoints if and only if all the null hypotheses on the primary endpoints are rejected.

For a mean absolute change from Baseline in total lesion counts of -35 for CB-03-01 cream and -13 for vehicle cream (standard deviation=17), sample size was calculated to be 13 subjects per treatment group.

For a mean percent change from Baseline in total lesion counts of -35 for CB-03-01 cream and -14 for vehicle cream (standard deviation=40), sample size was calculated to be 77 subjects per treatment group.

For a mean percent change from Baseline in non-inflammatory lesion counts of -33 for CB-03-01 cream and -5 for vehicle cream (standard deviation=40), sample size was calculated to be 43 subjects per treatment group.

For a mean percent change from Baseline in inflammatory lesion counts of -37 for CB-03-01 cream and -23 for vehicle cream (standard deviation=40), sample size was calculated to be 172 subjects per treatment group.

Based on those assumptions, at least 350 subjects in each treatment group (CB-03-01 cream, 1% BID and vehicle BID) will be included in each Phase 3 study to provide sufficient power (90%) with the chosen primary endpoints.

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. Summaries will be provided for each treatment group.

The Safety set will include all subjects who received at least one application of the test article. The ITT set will include all randomized subjects. The 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, with the ITT set considered as the primary set for statistical analysis. Multiple imputation will be used to impute missing values for the primary endpoints and absolute change in total lesions count (S1) in the ITT analyses. Sensitivity analyses will be performed to investigate the robustness of the results obtained on the ITT set for the primary endpoints (change from Baseline in non-inflammatory and inflammatory lesion counts and IGA "success" at Week 12). Missing values for the other secondary endpoints (i.e., S2-S4: percent change in lesions counts) will be calculated using the values obtained from the multiple imputation of the primary efficacy endpoints and secondary efficacy endpoint #1 (S1).

17.3.1 Efficacy Analyses

17.3.1.1 Primary Efficacy Analysis

Hypothesis tests on the primary endpoints will be conducted in hierarchical order for P1 through P3.

P1: A logistic regression model with treatment and analysis center as fixed effects will be used to compare the proportion of subjects achieving "success" in each treatment group at Week 12, where "success" is defined as an IGA score of "clear" (score=0) or "almost clear" (score=1) AND at least a two-point improvement in IGA compared to Baseline.

P2: An analysis of covariance (ANCOVA) will be used to compare the absolute change from Baseline in non-inflammatory lesion count in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline non-inflammatory lesion count as the covariate.

P3: An ANCOVA will be used to compare the absolute change from Baseline in inflammatory lesion count in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline inflammatory lesion count as the covariate.

17.3.1.2 Secondary Efficacy Analysis

Hypothesis tests on the secondary endpoints will be conducted in hierarchical order for S1 through S4.

S1: An ANCOVA will be used to compare the absolute change from Baseline in total lesion counts in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline total lesion count as the covariate.

S2: An ANCOVA will be used to compare the percent change from Baseline in total lesion counts in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline total lesion count as the covariate.

S3: An ANCOVA will be used to compare the percent change from Baseline in non-inflammatory lesion counts in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline non-inflammatory lesion count as the covariate.

S4: An ANCOVA will be used to compare the percent change from Baseline in inflammatory lesion counts in each treatment group at Week 12, with treatment and analysis center as fixed effects and the Baseline inflammatory lesion count as the covariate.

17.3.1.3 Imputation of Missing Data

Missing values for the primary endpoint in the ITT analyses will be imputed by

- Multiple imputation using missing at random assumption;
- Missing at worst value (for the entire set);
- Worst case;
- Last observation carried forward; and
- Baseline observation carried forward.

17.3.1.4 Sensitivity Analyses

Sensitivity analyses will be performed to investigate the robustness of the results obtained on the ITT set for the primary endpoints. The first sensitivity analysis will be the Per Protocol analysis. Four additional sensitivity analyses will be performed using different methods of imputation on the ITT set. On a per-subject basis, missing values for the primary endpoints will be imputed with the

1) Worst value (for the entire set);
2) Worst case;
3) Last observation carried forward; and
4) Baseline observation carried forward.

17.3.1.5 Multicenter Studies

Each center will conduct the clinical study under a common protocol. Consistency in study execution at each center will be emphasized. The study is to be conducted in such a manner as to have a minimum of eight ITT subjects enrolled in each of the treatment groups at each center (i.e., 16 ITT subjects enrolled overall per study center). In the event

that there are too few subjects in a treatment arm for a center, then this center's data will be combined with another center's data in order to achieve the desired minimum number of subjects per treatment arm. The combining of data across centers will be accomplished by combining data from two or more centers based on geographical and climatic similarities until the minimum number of subjects per treatment arm is achieved. The sequence of combination will be based on the total number of subjects enrolled in each center (combining the lowest with second lowest and so on). Combining center data to achieve sufficient subjects per treatment arm will result in combined centers. These combined centers, as well as individual centers with sufficient subjects per treatment arm, will be referred to as "analysis centers" in the statistical analysis.

17.3.1.6 Multiple Comparisons/Multiplicity

All the hypothesis tests for the primary endpoints have to be performed at the same significance level α=0.05 two-sided and the failure to reject a null hypothesis will imply the failure of rejecting of all the subsequent null hypotheses. This approach inflates the overall type II error β, which in the worst case scenario is equal to the sum of the Type II error β connected with the individual hypothesis tests.

The hypothesis test for the secondary endpoints will be performed at the same significance level α=0.05 two-sided of the primary endpoints if and only if all the null hypotheses on the primary endpoints are rejected.

17.3.1.7 Subgroup Analyses

No subgroup analyses are planned.

17.3.2 Treatment Compliance and Extent of Exposure Analyses

17.3.2.1 Treatment Compliance

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

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

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

Descriptive statistics will be used to summarize test article compliance at each visit and overall for the ITT and PP sets. The proportion of compliant and non-compliant subjects will be summarized by table of frequencies at each visit and overall for the ITT and PP sets. Subjects with an overall compliance not evaluable (due to missing data) or less than 80% will be excluded from the PP set.

17.3.2.2 Extent of Exposure

Descriptive statistics will be used to summarize exposure to test article for the ITT, PP and Safety 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 and summarized by treatment using descriptive statistics.

17.3.3 Safety Analyses

17.3.3.1 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 by treatment group and severity at each visit.

17.3.3.2 Adverse Events (AEs)

Pre-treatment AEs (PTAEs) and Treatment Emergent AEs (TEAEs) will be coded using the MedDRA coding dictionary. TEAEs will be summarized by treatment group and overall. The number and proportion of subjects with any TEAE and the number of TEAEs will be tabulated by MedDRA SOC and PT, seriousness, relationship to test article, and severity.

17.3.3.3 Electrocardiograms (ECGs)

ECGs will be evaluated for any material change during the study period. Results (normal/borderline/abnormal) of the ECG and descriptive statistics will be provided by treatment group at each visit for heart rate, RR duration, PR duration, QRS duration, QT duration including Bazett's and Fridericia's corrections, and P axis for the Safety set. Changes in overall interpretation (normal/abnormal/borderline) of the ECG from Baseline to Week 12 will be examined using shift tables.

17.3.3.4 Vital Signs

Vital signs will be listed and summarized by treatment group. Descriptive statistics (mean, standard deviation, CV%, minimum, median, and maximum) will be presented.

17.3.3.5 Urine Pregnancy Tests

The results of UPTs monthly at Visit 1 (Baseline), Visit 2 (Week 4), Visit 3 (Week 8), and Visit 4 (Week 12 / end of treatment), or if the subject withdraws prematurely, will be listed.

17.4 Interim Analyses

No interim statistical analyses are 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) 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 CRO.

The IRB approved consent/assent form must include all elements required by FDA, state, and local 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

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 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 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 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 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 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 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 CRO in the event of a FDA 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 CRO or the institution where the study is conducted, whichever is longer. The original Label Pages and Study Medication Accountability Logs will be collected at the end of the study and kept with the study records. Copies of these pages and logs will be kept at the sites.

The investigator must contact 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 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 CRO or the Sponsor, the FDA or other 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 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.

2. 171-7151-201. A Phase 2, Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Dose Escalating Study to Evaluate the Safety and Efficacy of Cortexolone 17α-Propionate (CB-03-01) Cream Applied Once or Twice-Daily for 12 Weeks in Subjects with Facial Acne Vulgaris. Intrepid Therapeutics, Inc., 2014.

APPENDIX 1 SAMPLE SUBJECT AND PARENT/GUARDIAN INSTRUCTION SHEET

Copies of the Subject Instruction Sheet on the next page will be provided to each study site. This sample instruction sheet may be used or modified by the investigator. If the instruction sheet is modified other than to reflect appropriate contact information specific to the site, the Subject Instruction Sheet will need to be reviewed and approved by the governing IRB prior to use as it will differ from the form included here which as part of the protocol is subject to IRB review and approval.

The investigator should provide a copy of the Subject Instruction Sheet to each subject and the subject's parent/guardian at Visit 1 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 about the study:

Contact:_____ At:_____

STUDY MEDICATION APPLICATION:

- YOU WILL BE INSTRUCTED HOW TO APPLY THE STUDY MEDICATION IN THE CLINIC **TWICE-DAILY: Once in the morning and once in the evening daily with approximately eight (8) hours or more between applications.**
- WASH YOUR ENTIRE FACE WITH MILD SOAP AND WATER AND GENTLY DRY THE AREA TO BE TREATED.
- WASH YOUR HANDS BEFORE AND AFTER APPLYING THE CREAM.
- 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.
- RECORD DATE AND TIME OF STUDY MEDICATION APPLICATION IN YOUR SUBJECT DIARY.
- DO NOT WASH THE TREATED AREA FOR AT LEAST FOUR (4) HOURS AFTER APPLICATION OR COVER OR WRAP AREAS WHERE STUDY MEDICATION WAS APPLIED.
- CONTINUE USE OF THE STUDY MEDICATION AS DIRECTED BY THE STUDY DOCTOR.

BEFORE EACH STUDY VISIT:

- **DO NOT APPLY THE STUDY MEDICATION WITHIN FOUR (4) HOURS OF YOUR SCHEDULED 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 2: Date: Time:	VISIT 3: Date: Time:
VISIT 4: 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 1 (Day 1, Baseline) and all follow-up visits as necessary.

SAMPLE SUBJECT DIARY for PROTOCOL CB-03-01/26

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, your used AND unused medication tubes at each visit. AS REQUIRED, PARENT/GUARDIAN SHOULD ASSIST IN RECORDING THE SUBJECT DIARY.

If you have any questions, call: **Name:** ______________________ **Telephone:** ____________________

Date (dd/MMM/yy)	Dose (time of day)		Date (dd/MMM/yy)	Dose (time of day)	
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
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___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm
___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm	___/___/___	___ ___ : ___ ___am	___ ___ : ___ ___pm

Next appointment: ____________, _____/_______/_____ at ________am/pm
Week Day **dd** **MMM** **yy**

Site Use Only:	***Diary Dispensed at Visit:*** ☐ **1 (Baseline)** ☐ **2 (Week 4)** ☐ **3 (Week 8)**	***Date Dispensed:***	***Date Returned:***

APPENDIX 3 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 of test article. Each subject will be assigned a subject number and provided with sufficient test article in standard packaging for the designated treatment period during the trial.

Subject Boxes and Labels
The randomization scheme will be blocked by investigational site. The box label will, at a minimum, contain the following information: protocol number, subject identifiers (subject number), the contents, an investigational test article disclaimer (e.g for US., Caution: New Drug Limited by United States law to investigational use), and the appropriate storage conditions for the test article.

Subject Kits and Labels
Each Subject Kit label will, at a minimum, contain the following information: protocol number, subject identifiers (subject number and subject initials to be filled in), the contents, the kit number, an investigational test article disclaimer (e.g. for US, Caution: New Drug Limited by United States law to investigational use), and the appropriate storage conditions for the test article. In the event of an emergency, the contents of the kit can be unblinded using the proper procedures as outlined in the protocol and by instructions provided to the site.

Kits will be dispensed at Baseline, Visit 2 (Week 4), and Visit 3 (Week 8). Subjects should not have more than one (1) kit at any time. When the kits are dispensed to subjects, the Subject Kit label should be completed entirely with the necessary information recorded in the Study Medication Accountability Log at the investigative site.

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

A 3.1 Test Article Storage and Preparation

Test articles will be stored under secure conditions until they are dispensed to the subjects. Test articles should be stored in accordance with the temperature specified on the box, kit, and tube labels.

A 3.2 Dispensing Test Article

Sites will receive shipments of one or more blocks of test articles. Subjects who are eligible for enrollment into the study will be assigned a three digit subject number by the study staff in ascending order beginning with the lowest available number.

The test article must be dispensed only to study subjects and only at study sites specified on the form FDA 1572 by authorized personnel as required by applicable regulations and guidelines.

On dispensing the test article for the first time on Day 1, provide each subject with sufficient test article for the designated treatment period and record the information on the Study Medication Accountability Log. Each tube contains approximately 30 grams of test article and should last for approximately two weeks.

The subject will also be instructed to bring all the tubes (used and unused) to each clinic visit. When a subject returns each used tube of test article, record the date of return, and initials of the individual accepting the return for each tube of test article on the same line of the Study Medication Accountability Log as the dispensing information.

At Visit 2 and Visit 3 (Week 4 and Week 8), visually check the tubes of test article to determine if the subject has applied correctly the test article and, if necessary, review the application instructions with the subject. Any discrepancies or concerns with the subject regarding the use of the diary to record test article compliance should be addressed.

At Visits 2, 3, and 4 (Weeks 4, 8 and 12), record the weights of all returned tubes to the nearest tenth gram (0.1 gram). At each visit, all tubes should be collected and additional tubes dispensed to the subject to ensure each subject has sufficient test article for the designated treatment period. Make every effort to obtain the return of all dispensed tubes of test article. If these efforts fail, make a detailed note of the reason for the failure in the source documents and on the Comments page of the CRFs.

A 3.3 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 (subject kit number).
- 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.

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 3.4 Dose Modifications

The subject should not modify the treatment regimen without consultation with the investigator. Subjects should be instructed to discontinue use if skin irritation or rash develops and to contact the study site. In the event that the investigator believes dose modification is necessary (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 3.5 Documentation of Application and Compliance

The date and time of the first application of test article will be recorded on the appropriate CRF. A CRF will also be used to record any changes from the application specified in the protocol (e.g., missed applications, investigator directed reduction in application frequency, etc.). The date and time of the last application of the test article will be recorded on a CRF.

A Subject Diary will be dispensed to subjects to record the dates and times of all application doses and to record any missed doses of the test article (Appendix 2). Subjects will be instructed to bring the diary with them to each study visit.

A 3.6 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 test article must be explained on the completed Study Medication Accountability Log. All returned tubes will be weighed to the nearest tenth gram (0.1g) 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 and copies of the CRF Label Pages containing the Subject Kit labels in the study file. A copy of the Study Medication Accountability Log and the CRF Label Pages with the original labels from the subject kits 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.