AN OPEN LABEL EVALUATION OF THE ADRENAL SUPPRESSION POTENTIAL AND TROUGH PLASMA CONCENTRATIONS OF CORTEXOLONE 17α-PROPIONATE (CB-03-01) CREAM APPLIED EVERY 12 HOURS FOR TWO WEEKS IN SUBJECTS 9 TO <12 YEARS OF AGE WITH ACNE VULGARIS

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SPONSOR:	Cassiopea S.p.A. Via C. Colombo 1, 20020 Lainate (MI), Italy
SPONSOR REPRESENTATIVES:	[redacted]
MEDICAL MONITOR:	[redacted]
PROJECT MANAGERS:	[redacted]

24 Hour Emergency Telephone Number

[redacted]

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PROTOCOL APPROVAL

The following individuals approve version 1.0 of the CB-03-01/28 protocol dated February 18, 2016. 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: 24 Febbr. 2016

Date: 23 Feb 2016

Date: 22 Feb 2016

Date: 22 feb 2016

Date: 22 feb -2016

Date: 23 FEB 2016

STUDY ACKNOWLEDGEMENT

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

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) or Ethics Committee(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-03-01/28 Site number: _____

Version: 1.0

Date of final version: February 18, 2016

PROTOCOL SYNOPSIS

Title	An Open Label Evaluation of the Adrenal Suppression Potential and Trough Plasma Concentrations of Cortexolone 17α-Propionate (CB-03-01) Cream Applied Every 12 Hours for Two Weeks in Subjects 9 to <12 Years of Age with Acne Vulgaris
Protocol Number	CB-03-01/28
Study Type	Phase 2
Test Article(s)	CB-03-01 cream containing 1% cortexolone 17α-propionate
Study Objective	The primary objectives of this study are to determine: a) the adrenal suppression potential and b) the trough plasma concentrations associated with topical application of CB-03-01 cream, 1% in subjects with acne vulgaris.
Study Design	An open label, multicenter study in children 9 to <12 years of age.
Treatment Groups	Eligible subjects will be dispensed CB-03-01 cream, 1% and will be instructed how and where to apply the test article to the face and trunk (see Section 6.2 for definition of the "Treatment Area") every 12 hours for two (2) weeks. Subjects will apply 2 grams of the test article. The test article will be applied by the subject or subject's parent/guardian in the clinic under supervision on Day 1 and Day 7 and at home for all other applications.
Duration of Treatment	Approximately 2 weeks
Duration of Study	Approximately 4-6 weeks
Study Population	Male and female subjects 9 to <12 years of age with moderate to severe facial acne vulgaris (Grade 3 or 4 on the Investigator's Global Assessment [IGA]) and obvious acne on the trunk (i.e., shoulder, upper chest, and/or back).
Total Number of Subjects	At least twenty (20) evaluable subjects. This may require the enrollment of approximately 24 subjects.
Number of Sites	Approximately six sites in the United States and Poland.
Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Subject is male or female, 9 to <12 years of age at the time of consent/assent. 2. Subject 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 written informed consent for the subject.

	3. Females of childbearing potential[1] must be using highly effective birth control methods[2,3] with a negative urine pregnancy test (UPT) at the Screening and Baseline Visits. 4. Subject has moderate to severe facial acne vulgaris (Grade 3 or 4) as determined by the Investigator's Global Assessment (IGA) [0 (clear) to 4 (severe) scale] and obvious acne on the trunk (i.e., shoulders, upper chest, and/or back) at the Screening Visit. 5. Subject has facial acne vulgaris with a minimum of 15 inflammatory lesions (papules, pustules, and nodules/cysts) and a minimum of 15 non-inflammatory lesions (open and closed comedones) at the Screening Visit. 6. Subject must be in general good health in the opinion of the investigator, with normal renal function as defined per protocol[4] and no clinically relevant abnormalities present at the screening physical examination, in the subject's medical history, or from safety laboratory tests (hematology, serum chemistry, and urinalysis). 7. Subject has normal adrenal function measured with a Cosyntropin Stimulation Test (CST) at Screening, defined as a normal pre-stimulation cortisol level and a 30-minute post-stimulation cortisol level of >18 µg/dL. 8. Subject and parent/guardian are able to communicate with the staff and are willing to comply with study instructions, reside at and/or return to the clinic for required visits.
Exclusion Criteria	A subject is ineligible to enter the study if he/she meets one or more of the following criteria: 1. Subject is pregnant, lactating, or is planning to become pregnant during the study. 2. Subject has a Body Mass Index (BMI) for age percentile >95% (see Appendix 5). 3. Except for the use of contraceptives, subject reported use of any prescription drug or herbal product within two (2) weeks of Visit 2 (Baseline), any non-prescription drug or vitamin or mineral supplements within one (1) week of Visit 2 (Baseline); any known enzyme-inducer,

[1] Females of childbearing potential are defined as subjects who have experienced menarche or are 10 years of age or older. Note: If a female becomes 10 years of age during the study, she must have a negative UPT at that time to continue study participation.
[2] Highly effective contraception includes: a) an intrauterine device (IUD) for at least one week prior to Visit 2 (Baseline); b) hormonal contraceptives (injections, implants, transdermal patch, vaginal ring); c) partner vasectomy (performed at least six months prior to Visit 2 [Baseline]); d) oral contraceptives WITH a barrier method: i) Male or female condom; diaphragm with spermicides; cervical cap with spermicides; contraceptive sponge; e) two barrier forms of contraception: i) male or female condom; ii) diaphragm with spermicides; iii) cervical cap with spermicides; iv) contraceptive sponge; OR f) total abstinence.
[3] Females taking hormonal therapy for any reason exclusive for the treatment of acne (e.g., as contraception, etc.) must be on 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 weeks prior to the start of the study.
[4] Normal renal function (per the requirement of inclusion criterion #6) is defined as a creatinine clearance of 80 mL/min or greater based on serum creatinine and the Cockcroft and Gault equation [1].

	enzyme-inhibitor, or reported chronic exposure to enzyme-inducers such as paint solvents or pesticides within 30 days of Visit 2 (Baseline). 4. Subject has used topical anti-acne medications containing retinoids such as tazarotene, adapalene, or tretinoin within four (4) weeks of Visit 2 (Baseline). 5. Subject has used the following systemic anti-acne medications: antibiotics within two (2) weeks of Visit 2 (Baseline), spironolactone within four (4) weeks of Visit 2 (Baseline), or retinoid therapy within three (3) months of Visit 2 (Baseline). 6. Subject has used topical corticosteroids (including inhaled and intranasal corticosteroids) within two (2) weeks of the CST at Visit 1 (Screening) and/or between Visit 1 (Screening) CST and Visit 2 (Baseline). 7. Subject has used systemic corticosteroids (including intramuscular and intralesional injections) within four (4) weeks of the CST at Visit 1 (Screening) and/or between the Visit 1 (Screening) CST and Visit 2 (Baseline). 8. Subject has used light treatments, microdermabrasion or chemical peels to the face, chest, and/or back within eight (8) weeks of Visit 2 (Baseline). 9. Subject has any skin or medical condition, including facial hair that could interfere with the evaluation of the test article or requires the use of interfering topical or systemic therapy. 10. Subject has any condition which, in the investigator's opinion, would make it unsafe for the subject to participate in this research study. 11. Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the study. 12. Subject cannot avoid any type of strenuous exercise (swimming, running, team sports, etc.) or the use of hot tubs/saunas from Visit 2 (Baseline) to the end of the study (Visit 4). 13. Subject has any clinically significant medical abnormality or chronic disease of the cardiovascular, gastrointestinal, respiratory, hepatic, or renal systems. This includes conditions (e.g., gastrointestinal surgery) that may interfere with metabolism or excretion. 14. Subject has a history of alcohol and/or drug abuse in the investigator's judgment or has a positive urine drug screen result at Visit 1 (Screening). 15. Subject is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function. 16. Subject is known to be hypersensitive to the test article or any components in the test article (see Section 6.1). 17. Subject has received an investigational drug or been treated with an investigational device within 30 days prior to Visit 2 (Baseline). 18. Subject is currently enrolled in an investigational drug or device study. 19. Subject has an irregular sleep schedule (cortisol levels exhibit physiological diurnal variation) as judged by the investigator. 20. Subject has experienced significant blood loss, as judged by the investigator, within 60 days or has donated plasma within 72 hours prior to Visit 2 (Baseline). 21. Subject tests positive at screening for human immunodeficiency virus (HIV) or is known to be seropositive for HIV. 22. Subject tests positive at Visit 1 (Screening) for hepatitis B surface antigen, hepatitis C antibody, or has a history of a positive result.

	23. Subject had major surgery within 30 days prior to Visit 2 (Baseline) or plans to have surgery during the study. 24. Subject has participated in a prior CB-03-01 clinical trial.
Study Procedures	The study will include a Screening Visit, a Baseline Visit, and two (2) scheduled follow-up visits. *DLT and Stopping Rules*: A Dose Limiting Toxicity (DLT) is defined as a systemic Grade 2 or higher (CTCAE, Version 4.0)[5] adverse event (AE) for which there is no clear alternative explanation of the cause of the AE. Non-systemic (local) AEs Grade 3 or higher for which there is no clear alternative explanation of the cause of the AE will also be considered DLTs. If more than 3 subjects within the study exhibit a DLT, enrollment will be stopped. Any subject who experiences a DLT, as described above, must discontinue treatment and be scheduled for a final visit. Any DLTs that are Grade 2 or greater systemic AEs with documented worsening from Baseline must be reported by the investigator immediately. 1. <u>Visit 1 (Days -45 to -14) – Screening Visit:</u> This visit will be scheduled such that the CST occurs between 7 AM and 9 AM. Screening labs will be collected with the subject fasting; if fasting laboratory tests are not possible, samples should still be collected, noting the protocol deviation. 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 be assigned a sequential subject screening number and begin screening procedures. Demographics, medical/dermatological history, and prior and concomitant medications and procedures will be reviewed with the subject. If a subject requires a "washout" period to meet inclusion/exclusion (I/E) criteria requirements, the subject will be required to return to the clinic to complete the remaining screening activities. Subjects not requiring a wash-out period from prohibited medications and procedures will undergo screening activities at this visit. Screening activities to determine subject eligibility include a review of the I/E criteria, a dermatologic exam, a physical examination (including vital signs, height, and weight), a UPT (if applicable), an electrocardiogram (ECG), routine safety laboratory tests (hematology, clinical chemistry, and urinalysis), drug and virus screens, clinical evaluations (including lesion counts and IGA [face only]), pharmacokinetic (PK) blood draw (for screening levels of plasma cortexolone 17α-propionate and cortexolone concentrations), and a CST performed between 7 AM and 9 AM to determine adrenal system response (i.e., Screening CST). Mild soap will be dispensed to the subject to use during the study and the subject will be instructed, to the extent possible, to wash or shower with the provided mild soap in the morning prior to the next visit. Note: Subjects who were consented for longer than 45 days prior to Baseline will be re-consented prior to enrolling into the treatment phase of the trial.

[5] NCI Common Terminology Criteria for Adverse Events, Version 4.0.

2. Visit 2 (Day 1) – Baseline Visit: **The Baseline Visit must be conducted at least 14 days and not more than 45 days after the Screening CST**. On Day 1, subjects with a normal response to CST (30-minute post-stimulation serum cortisol >18 µg/dL) who continue to meet all the other I/E criteria will be enrolled in the study. Facial lesion counts, IGA, and UPT (if applicable) will be performed prior to test article application. The severity of local skin reactions (LSRs) (telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus) will be documented for the face and trunk, separately, prior to test article application. Concomitant medications/procedures will be reviewed.

   Subjects will be assigned to the next available (lowest) subject number in ascending order. A PK blood draw will be performed before the initial application of the test article for baseline concentrations of cortexolone 17α-propionate and cortexolone in plasma.

   The subject and parent/guardian will be instructed on how to apply the test article to the face and trunk (see Section 6.2 for definition of the "Treatment Area"). The percent body surface area (BSA)[6] to be treated (face + trunk) will be recorded. The test article will be weighed prior to dispensing and the first dose will be applied in the clinic under supervision of the investigator or study staff. Subjects should not wash the Treatment Area for at least eight (8) hours after test article application and not apply any make-up or skin care products to the Treatment Area for at least four (4) hours after test article application. Subjects will also be instructed not to swim or participate in any other activities which could potentially remove the product from the Treatment Area for the duration of the study.

   Approximately 15 minutes after application of the test article, AEs and LSRs (face and trunk, separately) post-application will be assessed. Subjects including the parent/guardian will be instructed to apply the test article to the Treatment Area every 12 hours at approximately the same time each morning and evening until the next scheduled follow-up visit. The subject will be scheduled for the first follow-up visit; the timing of this visit (Visit 3) will occur so that the trough PK blood draw on Day 7 occurs 12 hours (± 30 minutes) after the evening application on Day 6.

3. Visit 3 (Day 7±1) – Follow-Up Visit: Subjects will return to the clinic for clinical evaluations (AEs and LSRs [face and trunk, separately]) and review of concomitant medications/procedures. Prior to the visit, subjects will be requested to i) apply the test article to the Treatment Area in the evening prior to the scheduled clinic visit and record the time (treatment to occur 12 hours (± 30 minutes) prior to the PK blood draw); ii) to the extent possible, wash or shower with the provided mild soap prior to arriving at the clinic; iii) withhold application of the test article on the morning of the visit; and iv) bring all tubes of test article to the

[6] BSA will be estimated based on the assumption that 1% BSA is equivalent to the area of the subject's hand with fingers held together.

	clinic for weighing. Subjects will have a trough PK blood draw in the clinic prior to the morning application of CB-03-01 cream, 1% for determination of plasma cortexolone 17α-propionate and cortexolone concentrations. Test article application will be reviewed with the subject and parent/guardian and additional test article will be dispensed, if necessary. Subjects will apply the test article to the Treatment Area in the clinic under staff supervision (and with assistance from parent/guardian, if necessary) and will be scheduled for the next follow-up visit; the timing of this visit (Visit 4) will occur so that the trough PK blood draw on Day 14 occurs 12 hours (± 30 minutes) after the evening application on Day 13. 4. Visit 4 (Day 14±2) – Final or End of Study (EOS) Visit: This visit will be scheduled such that the CST occurs between 7 AM and 9 AM and within one hour (±1) of the Screening CST. EOS safety laboratory test results will indicate if the subject was fasting (preferred) or not. Subjects will return early in the morning for clinical evaluations (IGA [face only], AEs, and LSRs [face and trunk, separately]), review of concomitant medications/procedures, and physical examination/vital signs. Prior to the visit, subjects will be requested to i) apply the test article to the Treatment Area in the evening prior to the scheduled clinic visit and record the time (treatment to occur 12 hours (± 30 minutes) prior to the PK blood draw); ii) withhold application of the test article on the morning of the visit; and iii) bring all tubes of test article to the clinic for weighing. Prior to the final application of the test article in the clinic, a CST will be performed within an hour (±1) of the Screening CST, ideally between 7 AM and 9 AM, to determine changes in the adrenal system response. Subjects will have a UPT (if applicable), an ECG, blood and urine collected for routine safety laboratory tests (hematology, clinical chemistry, and urinalysis), and a trough PK blood draw for determination of plasma cortexolone 17α-propionate and cortexolone concentrations. All tubes of test article will be collected. All subjects will be discharged from the study at this visit unless there is evidence of adrenal suppression. 5. Post-Treatment Follow-up Visits (Suppressed Subjects Only): Any subject who has evidence of adrenal suppression (30-minute post-stimulation serum cortisol level of ≤18 µg/dL) at Visit 4 (Day 14) or EOS will return for CST approximately every four (4) weeks BUT no sooner than four (4) weeks (28 days) after Visit 4, and subsequently about every four (4) weeks BUT no earlier than every four (4) weeks (≥28 days) thereafter until the adrenal response returns to normal (30-minute post-stimulation serum cortisol >18 µg/dL). During this period, the subject shall not use the test article or any steroid medication (topical or systemic).
Study Measurements	Acne severity will be assessed by the investigator as follows: • Investigator's Global Assessment (IGA): Overall severity of facial acne using a five-point scale from 0 = clear to 4 = severe will be evaluated at Screening, Baseline, and Day 14 (or EOS). This is a static morphological scale that refers to a point in time and not a comparison to Baseline.

- Acne Lesion Counts: Inflammatory lesions (papules, pustules and nodules/cysts) and non-inflammatory lesions (open and closed comedones) on the entire face will be counted and recorded separately at Screening and Baseline. Lesions on the trunk (i.e., shoulders, upper chest, and/or back) will not be counted.

Safety will be assessed by the investigator via the following:

- Physical examination/vital signs at Screening and Day 14 (or EOS);
- Safety laboratory tests (hematology, clinical chemistry, and urinalysis) at Screening and Day 14 (or EOS);
- UPTs (for all females of childbearing potential) at Screening, Baseline, and Day 14 (or EOS); and
- ECGs at Screening and Day 14 (or EOS).

The following additional safety parameters will be assessed.

Local Skin Reactions (LSRs): LSRs will be assessed by the investigator and the subject at Baseline (before and after the first test article application), Day 7, and Day 14 for the face and trunk, separately. Telangiectasia, skin atrophy, and striae rubrae will be assessed by the investigator using a five-point ordinal scale (0 = none, 1 = trace, 2 = mild, 3 = moderate, and 4 = severe). Erythema, edema, and scaling/dryness will also be assessed by the investigator using a five-point ordinal scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe). Subjects will be asked to rate the severity of stinging/burning using a four-point ordinal scale (0 = none, 1 = minimal, 2 = moderate, and 3 = severe) and pruritus using a four-point ordinal scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). Only LSRs that require medical intervention (e.g., prescription medication) or require withholding the application of the test article will be documented as AEs. In addition, any LSRs that are not listed above will be recorded as AEs.

Adverse Events (AEs): All local and systemic AEs will be recorded. At each visit, subjects will also be questioned specifically about the status of any new or ongoing AEs.

Cosyntropin Stimulation Test (CST): At Visit 1 (Screening), a CST will be performed for each subject between 7 AM and 9 AM. The Visit 4 (Day 14/EOS) CST will also be performed within one hour (±1) of the Screening CST and ideally also between 7 AM and 9 AM. Any subject who has an abnormal CST result (serum cortisol level $\leq$18 µg/dL) at Day 14 or EOS will return approximately every four (4) weeks thereafter for CST until the serum cortisol returns to normal.

PK Assessment: Eligible subjects will have a PK blood draw at Screening, Baseline, Day 7, and Day 14. For Day 7 and Day 14, all subjects will have blood drawn 12 hours (± 30 minutes) after the evening application on the prior day for assessment of "trough" cortexolone 17α-propionate and cortexolone concentrations in plasma.

Test Article Compliance: Test article applications on Day 1 and Day 7 will occur in the clinic under study staff supervision. The other test article doses will be applied by the subject or the subject's parent/guardian at home. The

	subject will be instructed to record the date and time of application on a diary. Subject diaries will be reviewed at follow-up visits to determine the doses of test article applied since the last visit and the subject will be counseled regarding compliance, if necessary. All dispensed tubes of CB-03-01 cream, 1% will be weighed at each visit and the amount of test article used will be recorded.
Study Endpoints	**Safety Endpoints:** *Primary Safety Endpoints* • Hypothalamic-Pituitary-Adrenal (HPA) Axis Response to Cosyntropin: Measurement of serum cortisol concentrations after stimulation of the adrenal cortex with Cosyntropin (CST) at Screening and Day 14 (or EOS). HPA axis suppression is defined as a post-stimulation serum cortisol level ≤18 µg/dL at Day 14 (or EOS). • Trough Plasma Concentrations: Trough measurements of cortexolone 17α-propionate and cortexolone concentration in plasma at Screening, Baseline, Day 7 and Day 14. *Secondary Safety Endpoints* • Safety laboratory testing (hematology, clinical chemistry, and urinalysis) at Screening and Day 14 (or EOS). • Local and systemic AEs at every visit (Baseline, Days 7 and 14). • The severity of the following LSRs [for face and trunk, separately]: telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus at Baseline (pre- and post-test article application), Day 7, and Day 14. • Physical examination/vital signs at Screening and Day 14 (or EOS). • UPTs (for all females of childbearing potential) at Screening, Baseline, and Day 14 (or EOS). • ECG at Screening and Day 14 (or EOS). **Efficacy Endpoints:** Due to the short duration of this PK study, no efficacy assessments/endpoints are planned. However, the overall severity of each subject's facial acne at the end of the study will be documented by the investigator or designee using the IGA score.
Sample Size Calculations	No formal power calculations were performed to establish the sample size. The number of evaluable subjects is historically consistent with other HPA/PK studies.
Statistical Methods	All statistical processing will be performed using SAS® unless otherwise stated. Excel or SAS® will be used for the analysis of trough plasma concentrations data. All subjects enrolled in the study who were dispensed and applied test article at least once will be included in the analysis of safety and will be considered the Safety population. Subjects who were discontinued from the study at Visit 2 (Baseline) due to abnormal screening laboratory test results or failure to meet any other eligibility criteria will be classified as screen failures and

	excluded from the HPA axis suppression summaries. Subjects with both Screening and Day 14 (or EOS) serum cortisol data (pre- and post-cosyntropin stimulation) who completed the study without significant protocol violations will be considered evaluable (Evaluable population). Subjects included in the PK analysis (PK population) must not have any significant protocol deviations, must have at least an 80% dose compliance based on number of applications, and must apply the final three doses as prescribed prior to the EOS PK assessment. Demographic and baseline characteristics will be summarized for the Safety, Evaluable, and PK populations. In addition, demographic variables, AEs, and primary reason for screen failure will be summarized separately for screen fail subjects. Frequency counts and percentages will be reported for categorical data and sample size, mean, standard deviation, median, minimum, and maximum will be reported for the continuous variables. **Safety Analyses:** ***Primary Safety Analyses*** HPA Axis Suppression Serum cortisol results will be summarized for evaluable subjects. HPA axis responses to CST will be dichotomized to normal and abnormal. An abnormal HPA axis response (HPA suppression) is defined as a 30-minute post-stimulation serum cortisol level of $\leq$18 µg/dL at Day 14. The proportion of subjects manifesting laboratory based evidence of adrenal suppression at Day 14 will be summarized and 95% confidence intervals for the proportion of abnormal responses will be derived. The changes in serum cortisol levels after stimulation at Screening and Day 14 (or EOS) will also be summarized. Pharmacokinetic Analysis Morning trough concentrations (C_{12}) of cortexolone 17α-propionate and cortexolone in plasma at Day 7 and Day 14 (prior to the morning test article application, where applicable) will be determined using validated methods. Descriptive statistics of the plasma concentrations will be provided at Screening, Baseline, Day 7 and Day 14 for each analyte. ***Secondary Safety Analyses*** Extent of Exposure to Test Article The total amount of CB-03-01 cream, 1% used (grams applied) will be calculated from the weights of the returned test articles. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be determined for the total amount of test article (grams) used by each subject in the Safety, PK, and evaluable populations. Dosing Compliance Descriptive statistics will be used to summarize test article compliance for the Safety, PK, and evaluable populations. Measures of test article compliance will include the duration of treatment, the total number of applications (determined from the actual number of applications reported by the subject), and the percent of expected doses applied. A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of the expected number of applications prior to the HPA assessment. Subjects included in the PK analysis (PK population) must not have any

	significant protocol deviations, must have at least an 80% dose compliance based on number of applications, and must apply the final three doses as prescribed prior to the end of study PK assessment. Safety Laboratory Tests Laboratory data collected at Screening and Day 14 (or EOS), including clinical chemistry, hematology, and urinalysis, will be tabulated for each visit and changes from Screening to Day 14 (or EOS) will also be tabulated for the Safety population. All laboratory data will also be listed. Data will be reported in units received from the central laboratory. Shift tables by analyte and by out of range flag will also be presented to facilitate the evaluation of change from Screening at Day 14 (or EOS). Local Skin Reactions (LSRs) The frequency distributions of the severity of LSRs associated with the topical application of corticosteroids and/or acne including telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus will be summarized with frequency counts and percentages at Baseline, Day 7, and Day 14 for face and trunk, separately. Adverse Events (AEs) All AEs reported during the study will be listed, documenting onset, whether therapy was required, any change in test article dosing, severity, possible relationship to test article, and outcome for the Safety population. Verbatim terms on the case report forms (CRFs) will be linked to preferred terms (PTs) and system organ class (SOC) using the MedDRA mapping system. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article. Urine Pregnancy Tests (UPTs) A listing of UPT results at Screening, Baseline, and Day 14 (or EOS) will also be prepared. Physical Examination/Vital Signs Physical examination findings at Screening and Day 14 will be recorded in medical history or as AEs. Vital signs will be recorded at Screening and Day 14. Electrocardiogram (ECG) ECGs will be evaluated at Screening and Day 14 (or EOS) for any material changes.

SCHEDULE OF EVENTS

PROCEDURES	Visit 1 Screening (Days -45 to -14)	Visit 2 Baseline Day 1	Visit 3 Day 7 ± 1	Visit 4 EOS[7] Day 14 ± 2
Informed Consent/Assent	X	X[8]		
Demographics	X			
Inclusion/Exclusion Criteria	X	Reconfirm eligibility		
Medical/Dermatological History	X			
Dermatologic Exam	X			
Physical Exam	X			X
Vital Signs, Height, and Weight[9]	X			X
UPT[10] (females of childbearing potential)	X	X		X
ECG	X			X
Safety Labs (Hematology, Chemistry and Urinalysis)[11]	X			X
Urine Drug Screen	X			
Virus Screen (HIV, HCV, HBV)	X			
Investigator's Global Assessment	Confirm eligibility	X		X
Lesion Counts	Confirm eligibility	X		
LSR Assessment		X (pre- & post-application)	X	X
PK Blood Draws[12]	X	X	X	X
Cosyntropin Stimulation Test (CST)[13]	X	Confirm eligibility		X
Study Medication Dispensed & Collected[14]		X	X	X
Study Treatment (q. 12 hours)		X	X[15]	
Percent BSA to be treated		X		
Weigh Test Article/Verify Compliance		X	X	X
AEs Evaluation	X	X	X	X
Review of Concomitant Medications & Procedures	X	X	X	X

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

ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
β-HCG	Beta-Human Chorionic Gonadotropin
b.i.d.	Twice a day
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CLIA	Clinical Laboratory Improvement Amendments
CFR	Code of Federal Regulations
CK	Creatine Kinase
CO_2	Bicarbonate
CRF	Case Report Form
CRO	Contract Research Organization
CST	Cosyntropin Stimulation Test
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data Clarification Form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EU	European Union
FDA	Food and Drug Administration
GGT	Gamma-Glutamyl Transferase
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-Pituitary-Adrenal
I/E	Inclusion/Exclusion
IEC	Institutional Ethics Committee
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine Device
LDH	Lactate Dehydrogenase
LSR	Local Skin Reaction
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter

mIU	Milli International Units
µg/dL	Micrograms/deciliter
NCI	National Cancer Institute
OTC	Over-the-Counter
PK	Pharmacokinetics
PT	Preferred Term
QA	Quality Assurance
RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
[redacted]	[redacted]
UPT	Urine Pregnancy Test
US	United States
USP	United States Pharmacopeia
WBC	White Blood Cells

TABLE OF CONTENTS

1. BACKGROUND

CB-03-01 (cortexolone 17α-propionate) is a steroidal antiandrogen that is being developed as a 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 [2_References].

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 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 vehicle, and (d) at 1% concentration applied b.i.d. are significantly more effective than its vehicle at reducing inflammatory and non-inflammatory lesions counts in adolescent and adult subjects.

Two Phase 3, randomized (1:1), double-blind, vehicle-controlled studies have been initiated in subjects 9 years of age and older with moderate to severe acne vulgaris. In each study, approximately seven hundreds subjects will be treated twice daily for 12 weeks with either CB-03-01 cream, 1% or vehicle cream.

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

This study was designed to investigate the safety (adrenal suppression effects and systemic concentrations of the drug product) of CB-03-01 cream, 1% in subjects 9 to <12 years of age with facial acne vulgaris. Adrenal suppression effects and systemic safety are an important safety concern. The current study was designed to investigate these concerns. Based on the results of Study 171-7151-202, a Phase 2, open label, maximal use HPA/PK study that was conducted in 42 subjects [twenty-two (22) adolescents (12 to <18 years of age) and twenty (20) adults (≥18 years of age)] with moderate to severe acne vulgaris of the face and chest/back (the "Treatment Area"), few subjects (1/20 adults [5.0%] and 2/22 [9.1%] adolescents) demonstrated laboratory evidence of adrenal suppression and no subjects demonstrated any clinical evidence of adrenal suppression [3_References]. Additionally, systemic exposure to CB-03-01 was low per the PK evaluation.

3. OBJECTIVE

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

4. STUDY DESIGN

This is an open-label, multicenter study in approximately 20 subjects 9 to <12 years of age with moderate to severe facial acne vulgaris (IGA score of 3 or 4) and obvious acne on the trunk (i.e., shoulders, upper chest, and/or back). The study will include a Screening Visit, a Baseline Visit, and two (2) scheduled follow-up visits. Eligible subjects will be dispensed CB-03-01 cream, 1% and will be instructed how and where to apply the test article to the face and trunk (see Section 6.2 for definition of the "Treatment Area") every 12 hours for two (2) weeks. Subjects will apply 2 grams of the test article per application. The test article will be applied by the subject or subject's parent/guardian in the clinic under supervision on Day 1 and Day 7 and at home for all other applications. The Medical Monitor will consider Dose Limiting Toxicity (DLT) when reviewing the safety data (see Section 8).

5. STUDY POPULATION

Male and female subjects 9 to <12 years of age with moderate to severe facial acne vulgaris (IGA of Grade 3 or 4) and obvious acne on the trunk (i.e., shoulder, upper chest, and/or back will be enrolled into the study. Subjects will be enrolled at approximately six sites in the United States and Poland.

5.1 Subject Eligibility

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

5.1.1 Inclusion Criteria

1. Subject is male or female 9 to <12 years of age at the time of consent/assent.
2. Subject 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 written informed consent for the subject.
3. Females of childbearing potential[16] must be using highly effective birth control methods[17,18] with a negative urine pregnancy test (UPT) at the Screening and Baseline Visits.
4. Subject has moderate to severe facial acne vulgaris (Grade 3 or 4) as determined by the Investigator's Global Assessment (IGA) [0 (clear) to 4 (severe) scale] and obvious acne on the trunk (i.e., shoulders, upper chest, and/or back) at the Screening Visit.
5. Subject has facial acne vulgaris with a minimum of 15 inflammatory lesions (papules, pustules, and nodules/cysts) and a minimum of 15 non-inflammatory lesions (open and closed comedones) at the Screening Visit.
6. Subject must be in general good health in the opinion of the investigator, with normal renal function as defined per protocol[19] and no clinically relevant abnormalities present at the screening physical examination, in the subject's medical history, or from safety laboratory tests (hematology, serum chemistry, and urinalysis).
7. Subject has normal adrenal function with a Cosyntropin Stimulation Test (CST) at Screening, defined as a normal pre-stimulation cortisol level and a 30-minute post-stimulation cortisol level of >18 µg/dL.
8. Subject and parent/guardian are able to communicate with the staff and are willing to comply with study instructions, reside at and/or return to the clinic for required visits.

[16] Females of childbearing potential are defined as subjects who have experienced menarche or are 10 years of age or older. Note: If a female becomes 10 years of age during the study, she must have a negative UPT at that time to continue study participation.
[17] Highly effective contraception includes: a) intrauterine device (IUD) for at least one week prior to Visit 2 (Baseline); b) hormonal contraceptives (injections, implants, transdermal patch, vaginal ring); c) partner vasectomy (performed at least six months prior to Visit 2 [Baseline]); d) oral contraceptives WITH a barrier method: i) Male or female condom; diaphragm with spermicides; cervical cap with spermicides; contraceptive sponge e) two barrier forms of contraception: i) male or female condom; ii) diaphragm with spermicides; iii) cervical cap with spermicides; iv) contraceptive sponge; OR f) total abstinence.
[18] Females taking hormonal therapy for any reason exclusive for the treatment of acne (e.g., as contraception, etc.) must be on 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 weeks prior to the start of the study.
[19] Normal renal function (per the requirement of inclusion criterion #6) is defined as a creatinine clearance of 80 mL/min or greater based on serum creatinine and the Cockcroft and Gault equation [1].

5.1.2 Exclusion Criteria

1. Subject is pregnant, lactating, or is planning to become pregnant during the study.
2. Subject has a Body Mass Index (BMI) for age percentile >95% (see Appendix 5).
3. Except for the use of contraceptives, subject reported use of any prescription drug or herbal product within two (2) weeks of Visit 2 (Baseline), any non-prescription drug or vitamin or mineral supplements within one (1) week of Visit 2 (Baseline); any known enzyme-inducer, enzyme-inhibitor, or reported chronic exposure to enzyme-inducers such as paint solvents or pesticides within 30 days of Visit 2 (Baseline).
4. Subject has used topical anti-acne medications containing retinoids such as tazarotene, adapalene, or tretinoin within four (4) weeks of Visit 2 (Baseline).
5. Subject has used the following systemic anti-acne medications: antibiotics within two (2) weeks of Visit 2 (Baseline), spironolactone within four (4) weeks of Visit 2 (Baseline), or retinoid therapy within three (3) months of Visit 2 (Baseline).
6. Subject has used topical corticosteroids (including inhaled and intranasal corticosteroids) within two (2) weeks of the CST at Visit 1 (Screening) and/or between Visit 1 (Screening) CST and Visit 2 (Baseline).
7. Subject has used systemic corticosteroids (including intramuscular and intralesional injections) within four (4) weeks of the CST at Visit 1 (Screening) and/or between the Visit 1 (Screening) CST and Visit 2 (Baseline).
8. Subject has used light treatments, microdermabrasion or chemical peels to the face, chest, and/or back within eight (8) weeks of Visit 2 (Baseline).
9. Subject has any skin or medical condition, including facial hair that could interfere with the evaluation of the test article or requires the use of interfering topical or systemic therapy.
10. Subject has any condition which, in the investigator's opinion, would make it unsafe for the subject to participate in this research study.
11. Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the study.
12. Subject cannot avoid any type of strenuous exercise (swimming, running, team sports, etc.) or the use of hot tubs/saunas from Visit 2 (Baseline) to the end of the study (Visit 4).
13. Subject has any clinically significant medical abnormality or chronic disease of the cardiovascular, gastrointestinal, respiratory, hepatic, or renal systems. This includes conditions (e.g., gastrointestinal surgery) that may interfere with metabolism or excretion.
14. Subject has a history of alcohol and/or drug abuse in the investigator's judgment or has a positive urine drug screen result at Visit 1 (Screening).
15. Subject is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
16. Subject is known to be hypersensitive to the test article or any components in the test article (see Section 6.1).
17. Subject has received an investigational drug or been treated with an investigational device within 30 days prior to Visit 2 (Baseline).

18. Subject is currently enrolled in an investigational drug or device study.
19. Subject has an irregular sleep schedule (cortisol levels exhibit physiological diurnal variation) as judged by the investigator.
20. Subject has experienced significant blood loss, as judged by the investigator, within 60 days or has donated plasma within 72 hours prior to Visit 2 (Baseline).
21. Subject tests positive at screening for human immunodeficiency virus (HIV) or is known to be seropositive for HIV.
22. Subject tests positive at Visit 1 (Screening) for hepatitis B surface antigen, hepatitis C antibody, or has a history of a positive result.
23. Subject had major surgery within 30 days prior to Visit 2 (Baseline) or plans to have surgery during the study.
24. Subject has participated in a prior CB-03-01 clinical trial

5.1.3 Subject Withdrawal Criteria

Procedures for handling subjects who are discontinued from the study are described in Section 14.2. Subjects who are discontinued will not be replaced; however, enrollment will continue until at least 20 evaluable subjects are achieved.

6. TEST ARTICLES AND REGIMEN

6.1 Description

CB-03-01 (cortexolone 17 α -propionate) Cream, 1% is an opaque topical formulation.

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, α-tocopherol, sodium edetate, polysorbate 80, citric acid monohydrate, purified water.

For test article labeling information refer to Appendix 3.

6.2 Instructions for Use and Application

Mild soap will be dispensed to the subject at Visit 1/Screening, which must be used for washing the Treatment Area and other areas of the body throughout the study; the subject must, at a minimum, begin using the provided mild soap in the morning prior to the clinic visit on Day 1 (i.e., Visit 2).

The subject and parent/guardian will be instructed to wash the area(s) to be treated (i.e., face and trunk) in the morning prior to clinic visits with the mild soap and water and then dry the area gently. At the clinic, the study staff will then instruct the subject and parent/guardian on how to dispense the test article and where to apply the test article. The

"Treatment Area" will be defined at Visit 2/Baseline by the investigator as the area to which the test article is applied and will include the face and trunk. The test article will be applied to the entire face and areas of the trunk (i.e., shoulders, upper chest, and/or upper back) where acne is present. The entire 2 grams of the test article must be applied; thus, if there is still test article remaining after the affected area of the trunk is treated, the test article will be applied to the adjacent skin. The subject will be instructed to apply the test article to this same Treatment Area with each application, regardless of whether acne is still present. The percent BSA[20] of the Treatment Area will be recorded at Baseline.

The first application of test article will be applied in the clinic under supervision of the study staff. The staff will dispense 2 grams of the test article; the subject will then be instructed (with assistance from parent/guardian, if necessary) to apply the test article to the defined Treatment Area using the "Dab, Spread, Pat" method of application. Subjects will be instructed to dab small amounts of the test article using a fingertip gently on the areas to be treated, then spread the test article to provide a thin, uniform layer over the entire Treatment Area, and finally to gently pat the skin until the test article has been absorbed into the skin. The study staff must assure that the subject (or with assistance from parent/guardian) is able to apply the test article to the entire Treatment Area (including the back).

Reminders for Each Application: The subject should wash the Treatment Area with the provided mild soap and water and then dry gently prior to application of the test article. The subject should not wash the Treatment Area for at least eight (8) hours after test article application and not apply any make-up or skin care products to the Treatment Area for at least four (4) hours after test article application. The subject will also be instructed not to swim or participate in any other activities which potentially could remove the product from the treated areas for the duration of the study.

The subject and parent/guardian will be provided with a Subject Instruction Sheet and a Subject Diary to record the dates and times of test article application on non-clinic days. **Note: The dispensing, recording, and application of test article by the subject may require adult supervision by the subject's parent/guardian.** The subject will be instructed to apply the test article only to the Treatment Area as instructed by the investigator or designated study personnel and to ask his/her parent/guardian for assistance, if needed. It should be emphasized to the subject that with each application of CB-03-01 cream, 1% the entire dosage must be applied for the entire study period, even if his/her acne begins to clear. The subject will be instructed to dispense 2 grams of the test article using the scale provided and apply the entire amount of the test article at home to the designated Treatment Area every 12 hours for two (2) weeks per the instructions from study staff on Day 1. The test article should be applied in the mornings and evenings at approximately the same time each day. The evening applications that will occur prior to a

[20] BSA will be estimated based on the assumption that 1% BSA is equivalent to the area of the subject's hand with fingers held together.

clinic visit (e.g., on Day 6 prior to Visit 3 and on Day 13 prior to Visit 4) must be applied 12 hours (± 30 minutes) prior to the PK blood draw; the study staff should instruct the subject what time to apply the test article on those days. The test article should be spread uniformly to cover the Treatment Area until all the test article is applied (regardless of whether acne is still present).

The subject will also be provided with instructions on how to store the test article at home during the study period. The subject will be instructed to bring all the containers of the test article (used and unused) and his/her completed diary 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 CRFs.

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

6.3 Warnings, Precautions and Contraindications

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

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

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

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

The effects of the test article in nursing mothers, pregnant women and their unborn children are unknown. Females must not be pregnant or planning a pregnancy during the study period. If the subject's mother is pregnant or nursing a glove should be worn when assisting the subject with test article application.

7. RANDOMIZATION ASSIGNMENT

There is no randomization assignment in this study. This is an open-label study in which all eligible subjects will be dispensed the test article at the Baseline Visit and provided with additional labeled test article during the study period. 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. Subject numbers will be included on the kits and the tubes for each subject. Enrollment will continue until 20 evaluable subjects are achieved.

8. DOSE LIMITING TOXICITY (DLT) AND "STOPPING RULES"

The Medical Monitor will consider Dose Limiting Toxicity (DLT) when reviewing the safety data. A DLT is defined as a systemic Grade 2 or higher (CTCAE, Version 4.0)[21] adverse event (AE) for which there is no clear alternative explanation of the cause of the AE. Non-systemic (local) AEs Grade 3 or higher for which there is no clear alternative explanation of the cause of the AE will also be considered DLTs. If more than 3 subjects within the study exhibit a DLT, enrollment will be stopped. Any subject who experiences a DLT, as described above, must discontinue treatment and be scheduled for a final visit. Any DLTs that are Grade 2 or greater systemic AEs with documented worsening from Baseline must be reported by the investigator immediately.

9. PRIOR AND CONCOMITANT THERAPIES

Any medications taken or therapies performed in the 90 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 prescription and over-the-counter (OTC) medications (including vitamins, herbs, and dietary supplements). Any changes in concomitant medications and/or therapies/procedures during the study must be recorded on the appropriate 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.

9.1 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 therapies/procedures as specified in Section 5.1.2.

During the study, subjects must not use any prescription or non-prescription drugs (including OTC acne treatments), vitamins, herbal products, and mineral supplements except for contraceptives.

9.2 Allowed Medications or Therapies

Subjects will be provided with a mild soap (Cetaphil® Gentle Skin Cleanser or equivalent), which must be used for washing the Treatment Area and other areas of the body throughout the study; the subject must, at a minimum, begin using the provided mild soap in the morning prior to the clinic visit on Day 1 (i.e., Visit 2). Skin care products (including make-up) must not be applied within four (4) hours of test article application.

[21] NCI Common Terminology Criteria for Adverse Events, Version 4.0.

No medications, including prescription drugs, herbal products, non-prescription drugs, mineral supplements, and vitamins are permitted during the study period as described in Section 5.1.2 without the knowledge and, if possible, permission of the investigator.

10. STUDY PROCEDURES

The study will consist of a Screening Visit, a Baseline Visit, and two (2) scheduled follow-up visits at Day 7 and Day 14. Specific activities for each study visit are listed below.

10.1 Visit 1 (Days -45 to -14): Screening Visit

Subjects can be screened for the study up to 45 days before Baseline. During Screening, the study requirements will be reviewed, written informed consent/assent obtained and eligibility confirmed. Screening labs will be collected with the subject fasting; if fasting laboratory tests are not possible, samples should still be collected, recording the protocol deviation. If applicable, the washout from prohibited medications or treatments will be determined and implemented. This visit will be scheduled such that the CST occurs between 7 AM and 9 AM.

At Screening, the investigator or designee will:

- Obtain a signed, written informed consent/assent. Subjects 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.
- Assign a sequential subject screening number.
- Complete demographics.
- Review eligibility criteria.
- Review and document medical/dermatological history.
- Record any prior or concomitant medications and therapies.
- Have subject complete washout from any prohibited medications, if necessary. The subject should return to the clinic to complete the remaining screening activities, if applicable. If the subject does not require a wash-out from prohibited medications and procedures, perform additional screening activities at this visit.
- Perform a dermatologic exam.
- Perform a physical exam (including vital signs, height, and weight).
- Perform a UPT for all females of childbearing potential[22] (Section 13.3). The results must be negative for the subject to be enrolled into the study.
- Perform a 12-lead ECG.
- Collect urine and blood samples for drug and virus screens and routine safety laboratory tests (see Sections 13.1 and 13.2). Laboratory tests will be collected with

[22] Females of childbearing potential are defined as subjects who have experienced menarche or are 10 years of age or older.

the subject fasting; if fasting laboratory tests are not possible, samples should still be collected, recording the protocol deviation.
- Perform clinical evaluations (IGA and acne lesion counts [face only]) to determine subject eligibility (see Section 11).
- Collect PK blood draw for screening levels of plasma cortexolone 17α-propionate and cortexolone concentrations (see Section 13.4).
- Perform a CST (see Section 13.5). CST will be performed between 7 AM and 9 AM at this visit.
- Inform the subject that if the CST results are not within the normal range, he/she will not be eligible for the study.
- Confirm the subject meets the inclusion/exclusion criteria (pending drug screen, laboratory test results, and CST results).
- Dispense mild soap to the subject and instruct the subject and parent/guardian to wash the face and trunk with the provided soap in the morning prior to the next clinic visit.

Once the Screening procedures have been completed, the investigator or designee will schedule a Baseline Visit. Note: Subjects who were consented for longer than 45 days will need to be re-consented prior to enrolling into the treatment phase of the trial.

10.2 Visit 2 (Day 1): Baseline Visit

The Baseline Visit must be conducted at least 14 days and not more than 45 days after the Screening CST.

At this visit, the investigator or designee will:
- Obtain a new signed, written informed consent/assent (if this visit is more than 45 days from Screening Visit).
- Query the subject and record any changes in concomitant medications and therapies.
- Review laboratory test and CST results and reconfirm that the subject meets the inclusion/exclusion criteria.
- Perform Baseline clinical evaluations (IGA and acne lesion counts [face only]) (see Section 11).
- Perform a UPT for all females of childbearing potential[22] (see Section 13.3). The results must be negative for the subject to be enrolled into the study.
- Assign the subject to the next available (lowest) subject number.
- Record any baseline LSRs, for the face and trunk separately, prior to application of the test article (see Section 11.3).
- Collect PK blood draw for baseline levels of plasma cortexolone 17α-propionate and cortexolone concentrations (see Section 13.4).
- Weigh and dispense initial tube(s) of test article and complete the Study Medication Accountability Log.

- Dispense the Subject Instruction Sheet to the subject (Appendix 1).
- Dispense the Subject Diary (Appendix 2) to the subject and provide completion instructions.
- Dispense and weigh 2 grams of the test article into a disposable container and provide to subject for application.
- Instruct the subject where and how to apply the initial dose of test article and define the "Treatment Area" (entire face and affected areas of the trunk including adjacent areas, as needed; see Section 6.2).
- Record the areas of the trunk that were treated and the total percent BSA (face + trunk) that was treated. Estimate BSA based on the assumption that 1% BSA is equivalent to the area of the subject's hand with fingers held together.
- Approximately 15 minutes after application, record any AEs and LSRs (for face and trunk, separately) after the initial application of the test article.
- Instruct the subject to apply the test article to the Treatment Area every 12 hours (i.e., in the **morning and evening**) at approximately the same time each day until the next scheduled follow-up visit.
- Schedule Visit 3 (Day 7). The timing of this visit will occur so that the trough PK blood draw on Day 7 occurs 12 hours (± 30 minutes) after the evening application on Day 6.

10.3 Visit 3 (Day 7±1): Follow-Up Visit

Subjects should, to the extent possible, shower or wash the treated areas with the provided mild soap in the morning prior to the visit and should not apply the test article at home on the day of the visit.

At this visit, the investigator or designee will:

- Query the subject and record any changes in health status (i.e., AEs) or concomitant medications and therapies.
- Record any LSRs (for face and trunk, separately).
- Collect trough PK blood draw for levels of plasma cortexolone 17α-propionate and cortexolone concentrations (see Section 13.4). PK blood draw will occur 12 hours (± 30 minutes) after the evening application on the prior day.
- Collect, dispense, and weight tube(s) of test article, as needed, and complete the Study Medication Accountability Log.
- Dispense the Subject Instruction Sheet to the subject, if needed (Appendix 1).
- Dispense (new) Subject Diary (Appendix 2), if necessary, to the subject.
- Dispense and weigh 2 grams of the test article into a disposable container and provide to subject for application.
- Apply test article to the "Treatment Area" under study staff supervision (see Section 6.2).

- Instruct the subject to apply the test article to the Treatment Area every 12 hours (i.e., in the **morning and evening**) at approximately the same time each day until the next scheduled follow-up visit.
- Schedule Visit 4 (Day 14). The timing of this visit will occur so that the trough PK blood draw on Day 7 occurs 12 hours (± 30 minutes) after the evening application on Day 13.

10.4 Visit 4 (Day 14±2): Final or End of Study Visit

This visit will be scheduled such that the CST occurs between 7 AM and 9 AM and within one hour (±1) of the Screening CST. Laboratory test results will indicate if the subject was fasting (preferred) or not.

At this visit, the investigator or designee will:

- Query the subject and record any changes in health status (i.e., AEs) or concomitant medications and therapies.
- Record any LSRs (for face and trunk, separately).
- Perform clinical evaluation (IGA) (see Section 11.1).
- Perform a physical exam (including vital signs).
- Perform a CST (see Section 13.5). CST will be performed between 7 AM and 9 AM and within one hour (±1) of Screening.
- Perform routine laboratory tests (see Section 13.1).
- Collect trough PK blood draw for levels of plasma cortexolone 17α-propionate and cortexolone concentrations (see Section 13.4). PK blood draw will occur 12 hours (± 30 minutes) after the evening application on the prior day.
- Perform a 12-lead ECG.
- Perform a UPT for all females of childbearing potential[23] (Section 13.3).
- Collect and weight tube(s) of test article, as needed, and complete the Study Medication Accountability Log.
- Discharge the subject from the study, unless there is evidence of adrenal suppression.
- Note: Medication restrictions as outlined in Section 9.1 are no longer required, with the exception of those medications that may affect adrenal function. Remind subjects not to use any medication that may affect adrenal axis function including topical corticosteroids (including inhaled and intranasal corticosteroids) or systemic corticosteroids (including intramuscular and intralesional injections) until the CST results are known. For those subjects with laboratory evidence of adrenal suppression, they must continue off such therapy and follow-up as designated in Section 10.5.

[23] Females of childbearing potential are defined as subjects who have experienced menarche or are 10 years of age or older.

- Review safety laboratory test results including serum cortisol levels, and complete the End of Study Form, unless the subject has an abnormal HPA axis response or any laboratory tests that need to be repeated, then follow the procedures in Section 10.5.

10.5 Post-Treatment Follow-Up Visits

These visits are only required for subjects who have demonstrated abnormal CST results at the end of study and are returning for the follow-up CST per Section 13.5. This visit should take place every four (4) weeks BUT no sooner than four (4) weeks (28 days) after Visit 4, and subsequently about every four (4) weeks BUT no earlier than every four (4) weeks (28 days) thereafter until the adrenal response returns to normal (30-minute post-stimulation serum cortisol >18 µg/dL).

At this visit, the investigator or designee will:

- Observe/query the subject about any changes in health status (AEs, concomitant medications, etc.) since previous visit. Document the findings on the appropriate AE or Concomitant Medication forms, as required.
- Perform the CST. If possible, the CST should be initiated between 7AM and 9 AM and within one hour (±1) of the Screening CST (see Section 13.5).
- If the subject has a normal HPA axis response, complete the End of Study Form.
- If the subject has an abnormal HPA axis response, notify the subject that he/she will need to return to the clinic in approximately four (4) weeks. Remind the subject that he/she is prohibited from using any medication that may affect adrenal axis function including topical, inhaled, intranasal, or systemic (including intramuscular and intralesional) corticosteroids.
- Repeat the CST every approximately four (4) weeks until HPA axis response has returned to normal and is documented as such.

11. CLINICAL EVALUATIONS

IGA and acne lesion counts will be performed to document the severity of acne on the face at the Screening and Baseline visits as part of the I/E criteria. IGA will be performed again at the Final Visit (EOS). The same investigator should complete the evaluations for all subjects screened and enrolled into the study. If this becomes impossible a sub-investigator with overlapping experience with the study should complete the IGA evaluations.

11.1 Investigator's Global Assessment (IGA)

Overall severity of acne on the face using a five-point scale from 0 = clear to 4 = severe will be conducted at the Screening, Baseline, and EOS visits. This is a static morphological scale that refers to a point in time and not a comparison to Baseline. Eligible subjects should also have obvious acne on the trunk (i.e., shoulder, upper chest and/or back), but these areas will not be included in the IGA.

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

11.2 Acne Lesion Counting

The number of inflammatory lesions (papules, pustules and nodules/cysts) 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 at the Screening and Baseline visits. Eligible subjects must have obvious acne on the trunk (i.e., shoulder, upper chest and/or back), but the number and type of lesions on the trunk will not be counted.

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/cysts- Any circumscribed, inflammatory masses greater or equal to 5mm in diameter with or without cystic changes.

11.3 Local Skin Reactions

LSRs will be collected separately for the face and trunk. At Days 1 (before and after first application), 7, and 14, the investigator or designee will document the presence 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).

The investigator or designee will also evaluate the severity of erythema, edema, and scaling/dryness using the five-point ordinal scales described below.

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

At Days 1 (before and after first application), 7, and 14, the subject will be asked to rate the severity of any stinging/burning and pruritus that occurred in the Treatment Area using the four-point scales described below.

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 article will be documented as AEs. Any LSRs that are not listed above will be recorded as AEs.

12. PHOTOGRAPHY

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

13. LABORATORY TESTS

13.1 Blood Chemistries, Hematology, and Urinalysis

Blood and urine specimens for chemistry, hematology, and urinalysis will be collected at the Screening Visit (Days -45 to -14) and Day 14 (or at EOS / early termination) for all subjects. Laboratory test results will indicate if the subject was fasting. Screening laboratory tests will be collected with the subject fasting and EOS laboratory tests are preferred to be in a fasting state.

The following tests will be performed:

SAFETY LABORATORY TESTS		
Chemistries	**Hematology**	**Urinalysis**
Albumin	WBC	Specific gravity
Alkaline phosphatase	RBC	pH
ALT (SGPT)	Hemoglobin	Glucose
AST (SGOT)	Hematocrit	Blood
Bilirubin, total	MCV	Ketones
BUN	MCH	Microscopic analysis
CO_2 (bicarbonate)	MCHC	WBCs
Chloride	Platelet count	RBCs
Cholesterol, total	RDW	Casts
Creatinine	Differential	
Glucose	Neutrophils	
LDH	Lymphocytes	
Potassium	Eosinophils	
Sodium	Monocytes	
Total protein	Basophils	
Triglycerides		
Uric acid		
GGT		
CK		

Sample collection, handling, labeling, and shipping should be done following the instructions provided by the relevant certified laboratory and the applicable local regulations.

The investigator must review all the subject's laboratory reports in a timely manner. **Note:** The investigator will initial and date each laboratory report to indicate his/her review. The investigator will note, directly on the laboratory report, whether or not any abnormal test results are clinically significant. The investigator must complete an appropriate AE form for any new or worsening abnormal test results that are identified as clinically significant after Baseline.

AEs that may be associated with venipuncture and that must be included in the informed consent/assent include:

- Pain

- Bruising
- Bleeding at the puncture site
- Fainting
- Inflammation of the vein

13.2 Drug and Virus Screening

At the Screening Visit, the urine and blood samples will be taken for:

Standard Drug Panel: Urine drug screen for barbiturates, benzodiazepines, opioids, cocaine, cannabinoids, and amphetamines. Result must be negative at Screening.

Virus Screen: Serology screen in blood for the detection of antivirus antibodies for human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV) surface antigen. Result must be negative at Screening for inclusion into the study.

Sample collection, handling, labeling and shipping should be done following the instructions provided by the relevant certified laboratory and the applicable local regulations.

13.3 Urine Pregnancy Tests

The UPTs will be performed at the study site, if the site is registered and conforms to CLIA regulations for such testing (possesses a current valid CLIA Certificate of Waiver), or at an appropriately registered reference laboratory. A UPT will be performed on all females of childbearing potential[24] at Screening, Baseline, and Day 14 (or EOS). The investigator will report the UPT results on the CRFs, in the subject's medical records, and in independent records maintained at the study site. The UPT used must have a minimum sensitivity of 25 mIU of β-HCG/mL.

13.4 Plasma Sample Collection

One of the objectives of the study is to determine the trough plasma concentrations of cortexolone 17α-propionate and cortexolone associated with the topical application of CB-03-01 cream, 1% in subjects with acne vulgaris.

13.4.1 Plasma Sample Collection

Blood will be collected at each visit (Screening, Baseline, Day 7, and Day 14) immediately prior to the application of the test article (if applicable). Concentrations of cortexolone 17α-propionate and cortexolone will be determined. The method of blood sample collection for

[24] Females of childbearing potential are defined as subjects who have experienced menarche or are 10 years of age or older.

trough PK analysis is detailed in the laboratory manual to be provided by the bioanalytical laboratory.

13.4.2 Plasma Storage

Each plasma sample will be divided into two pre-labeled and pre-cooled polypropylene tubes and placed on dry ice and acetone until final storage in an ultra-low freezer as specified in the laboratory manual.

Each sample tube will be identified with a label resistant to storage temperature. Please refer to the laboratory manual for specific instructions related to the labeling and management of these specimens.

13.4.3 Specimen Shipment

On request, site staff personnel shall ship one of the duplicate samples of plasma frozen under dry ice. The secondary plasma sample will be retained in an ultra-low freezer as specified in the laboratory manual as back-up samples until confirmation that the initial shipment has been received safely by the analytical laboratory.

Samples will be shipped by an authorized courier to:

[redacted]

The study site shall retain copies of the shipping documents generated at the time of shipment. Refer to the laboratory manual for additional detailed instructions related to the labeling and management of these specimens.

13.4.4 Analytical Methodology

The concentrations of cortexolone 17α-propionate (CB-03-01) and cortexolone will be determined in the plasma samples using validated analytical methods for each analyte [4, 5].

13.5 Cosyntropin Stimulation Test

At Visit 1 (Screening), a CST will be performed for each subject between 7 AM and 9 AM.

At Visit 4 (or EOS), a CST (and any follow-up CSTs) will be performed within ± one hour of the screening CST and ideally between 7 AM and 9 AM.

Perform the CST as follows (see Appendix 4):

- Collect a pre-stimulation blood sample as specified in the Laboratory Manual.

- Reconstitute one vial of cosyntropin (0.25mg) in sodium chloride for injection USP (the volume of sodium chloride in the package insert for Cortrosyn® is 2 to 5mL).
- Inject the cosyntropin intravenously (the length of time during which the cosyntropin should be injected is 2 minutes).
- Thirty (30) minutes after completing the cosyntropin injection, collect a post-stimulation blood sample as specified in the Laboratory Manual.

If the results of the Visit 1 (Screening) CST indicate the subject has an abnormal HPA axis response (defined as a post-stimulation serum cortisol level of ≤18µg/dL), the subject will be classified as a screen failure and withdrawn from the study following the procedures in Section 14.4. In addition, direct the subject to consult with their physician concerning the abnormality unless the investigator believes it is not medically indicated. The conversation with the subject must be documented in the source documents.

If a subject's EOS laboratory results show an abnormal HPA axis response (defined as a post-stimulation serum cortisol level of ≤18 µg/dL), the test article will be considered to have caused the abnormal CST result in the subject. Report this abnormality as an AE. Instruct the subject not to use ANY topical or systemic steroids; however, other therapies that will not affect their adrenal function may be used to treat their acne. The subject should be scheduled to return for a follow-up visit no less than four (4) weeks after the EOS laboratory samples are collected. In the event the subject is still found to have laboratory evidence of adrenal suppression, the subject will be required to return for additional follow-up visits, no less than every four (4) weeks, until the HPA axis response has been documented to return to normal.

AEs that may be associated with the CST and that must be included in the informed consent/assent include:

- Rare hypersensitivity reactions
- Bradycardia
- Tachycardia
- Hypertension
- Peripheral edema
- Rash

AEs associated with venipuncture and that must also be included in the informed consent/assent include those listed in Section 13.1.

14. 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.

14.1 Completion of the Study

Each subject who completes the course of treatment as specified in this protocol will have completed the study.

14.2 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 withdraw. NOTE: if the subject 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
- Progressive disease
- Noncompliance with study drug
- Protocol deviation
- Pregnancy (if applicable)
- Lost to follow-up
- Study terminated by Sponsor
- Death

If a subject withdraws from the study prematurely for any reason, every attempt should be made to complete the EOS procedures prior to discharging the subject from the study. If a subject withdraws prematurely during the treatment period for any reason, the Visit 4 procedures (minus the PK blood draw) will be completed. Subjects who withdraw prematurely will be replaced until at least 20 subjects with both Screening and Day 14 serum cortisol data (pre- and post-cosyntropin stimulation) have completed the study without any significant protocol violations (i.e., evaluable subjects). When a subject is withdrawn from the study for a treatment-related AE (i.e., possibly, probably or definitely related as defined in Section 15.1), when possible, the subject should be followed until resolution of the AE.

14.3 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.

14.4 Screen Failures

A subject will be considered a screen failure if Visit 1/Screening laboratory results indicate (1) an abnormal pre-CST serum cortisol level, (2) abnormal HPA axis function (a low post-CST serum cortisol level), or (3) other clinically significant out-of-range laboratory test results, in the opinion of the investigator. If these conditions apply, the subject should be excluded from study participation, and the Screen Failure CRF should be completed. No clinical evaluation or follow-up CST will be performed in these subjects.

If a subject withdraws prematurely during the treatment period for another reason, complete the CRF for the appropriate visit, then complete the End of Study CRFs including scheduling appropriately to obtain the End of Study CST.

Subject enrollment will continue until at least 20 evaluable subjects with both Screening and Day 14 serum cortisol data (pre- and post-cosyntropin stimulation) have completed the study without any significant protocol violations (evaluable subjects). This may require the enrollment of approximately 24 subjects.

15. 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 an 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) or Institutional Ethics Committee (IEC) 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 the contract research organization (CRO) in identifying any untoward medical occurrence, thereby allowing:

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

Test article is defined as a pharmaceutical form of an active ingredient (or "primary operational component" for devices) 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).

15.1 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.

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.

15.2 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 serious AEs are:

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

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

Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In this case, the investigator must immediately report the event to the Sponsor. In addition, such information should also be provided to the site's respective IRB/IEC 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 a SAE (regardless of its relationship to test article) that occurs within 30 days after stopping the test article, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to the CRO, if available.

As required, the CRO will notify participating investigators of all suspected adverse reactions that are serious and unexpected. This notification will be in the form of an IND 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/IEC according to local regulations. The investigator and IRB/IEC will determine if the informed consent/assent requires revision. The investigator should also comply with the IRB/IEC 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.

15.3 Laboratory Test Abnormalities

In addition to being recorded on the appropriate laboratory test results CRF, or being electronically submitted from a central laboratory, any clinically significant laboratory test result that meets the criteria for an AE (see Section 15) or SAE (see Section 15.2) must also be recorded on the AE CRF. SAEs must be reported to the Sponsor and IRB/IEC as per Section 15.2. In these cases, the CRO will typically require additional information about the clinically significant abnormality, including information regarding relationship to test article or other causes, any action taken, and resolution. Other laboratory test abnormalities will be addressed by the investigator on the actual laboratory test reports, and on the associated laboratory test results CRF.

15.4 Pregnancy

Females of childbearing potential will be defined as subjects who have experienced menarche or are 10 years of age or older. All females of childbearing potential must have a negative pregnancy test prior to study enrollment, and must use a highly effective[25]

[25] Highly effective contraception includes a) total abstinence, b) oral, injected, or implanted hormonal methods of contraception, c) IUD, d) partner vasectomy (performed at least six (6) months prior to study entry), e) oral contraceptive WITH a barrier method, or f) double barrier methods of contraception [barrier

method of contraception during the course of the study, in a manner such that risk of failure is minimized. Note: If a female becomes 10 years of age during the study, she must have a negative UPT at that time to continue study participation. Prior to study enrollment, females 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.

Females should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). 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 receive or apply further test article and must be discontinued from the study.

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

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

16. BLINDING/UNBLINDING

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

methods include male or female condom, diaphragm with spermicidal foam/gel/film/vaginal suppository, cervical cap with spermicides, or contraceptive sponge].

17. CLINICAL SUPPLIES

17.1 Test Article Information

Test articles will be packaged and labeled by the Sponsor or designee. Detailed information on the packaging/labeling, storage and preparation, dispensing, accountability, etc. is included in Appendix 3.

17.2 Supplies Provided by Sponsor or Sponsor's CRO

- eCRFs
- Subject Diaries
- Source document draft templates
- Site regulatory binder
- UPT kits (for US sites)
- CST kits or equivalent (see Appendix 4)
- Weighing scales (if necessary)
- Mild soap cleanser or equivalent

17.3 Supplies Provided by Investigator

- Urine collection containers for UPTs
- Refrigerated centrifuge to process blood samples
- Ultra-low freezer for storage of plasma samples

17.4 Supplies Provided by the Clinical Laboratory

- Supplies to collect and transport urine and blood samples to the clinical laboratory
- Polypropylene tubes and labels for plasma aliquots for PK analysis
- Urine collection containers
- UPT kits (for EU sites)

18. STATISTICAL CONSIDERATIONS

18.1 Sample Size

No formal power calculations were performed to establish the sample size. The number of evaluable subjects is historically consistent with other HPA/PK studies in this age range.

18.2 Endpoints

18.2.1 Efficacy Endpoints

Efficacy will not be assessed in this study.

18.2.2 Safety Endpoints

Primary Safety Endpoints

- HPA Axis Response to Cosyntropin: Measurement of serum cortisol concentrations after stimulation of the adrenal cortex with cosyntropin (CST) at Screening, and Day 14 (or EOS). HPA axis suppression is defined as a post-stimulation serum cortisol level ≤18 µg/dL at Day 14 (or EOS).
- Trough Plasma Concentrations: Trough measurements of cortexolone 17α-propionate and cortexolone in plasma at Screening, Baseline, Day 7 and Day 14.

Secondary Safety Endpoints

- Safety laboratory testing (hematology, clinical chemistry, and urinalysis) at Screening and Day 14 (or EOS).
- Local and systemic AEs at every visit (Baseline, Days 7 and 14).
- The severity of the following LSRs [for face and trunk, separately]: telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning and pruritus will be documented at Baseline (pre- and post-test article application), Day 7, and Day 14.
- Physical examination/vital signs at Screening and Day 14 (or EOS).
- UPTs (for all females of childbearing potential) at Screening, Baseline, and Day 14 (or EOS).
- ECG at Screening and Day 14 (or EOS).

18.3 Statistical Methods

All statistical processing will be performed using SAS® unless otherwise stated. Excel or SAS® will be used for the analysis of trough plasma concentrations data.

All subjects enrolled in the study who were dispensed and applied test article at least once will be included in the analysis of safety and will be considered the Safety population. Subjects who were discontinued from the study at Visit 2 (Baseline) due to abnormal screening laboratory test results or failure to meet any other eligibility criteria will be classified as screen failures and excluded from the HPA axis suppression summaries. Subjects with both Screening and Day 14 (or EOS) serum cortisol data (pre- and post-cosyntropin stimulation) who completed the study without significant protocol violations will be considered evaluable (Evaluable population). Subjects included in the PK analysis (PK population) must not have any significant protocol deviations, must have at least an 80% dose compliance based on number of applications, and must apply the final three doses as prescribed prior to the EOS PK assessment.

Demographic and baseline characteristics will be summarized for the Safety, Evaluable, and PK populations. In addition, demographic variables, AEs, and primary reason for screen failure will be summarized separately for screen fail subjects. Frequency counts and

percentages will be reported for categorical data and sample size, mean, standard deviation, median, minimum, and maximum will be reported for the continuous variables.

18.3.1 Efficacy Analyses

There will be no efficacy analyses.

18.3.2 Safety Analyses

18.3.2.1 HPA Axis Suppression

Serum cortisol results will be summarized for the evaluable subjects. HPA axis responses to CST will be dichotomized to normal and abnormal. An abnormal HPA axis response (HPA suppression) is defined as a 30-minute post-stimulation serum cortisol level of <18 µg/dL at Day 14. The proportion of subjects manifesting laboratory based evidence of adrenal suppression at Day 14 will be summarized and 95% confidence intervals for the proportion of abnormal responses will be derived. The changes in serum cortisol levels after stimulation at Screening and Day 14 (or EOS) will also be summarized.

18.3.2.2 Pharmacokinetic Analysis

Morning trough concentrations (C_{12}) of cortexolone 17α-propionate and cortexolone in plasma at Day 7 and Day 14 (prior to the morning test article application, where applicable) will be determined using validated methods. Descriptive statistics of the plasma concentrations will be provided at Screening, Baseline, Day 7, and Day 14 for each analyte.

18.3.3 Secondary Safety Analysis

18.3.3.1 Extent of Exposure to Test Article

The total amount of CB-03-01 cream, 1% used (grams applied) will be calculated from the weights of the returned test articles. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be determined for the total amount of test article (grams) used by each subject in the Safety, PK, and evaluable populations.

18.3.3.2 Dosing Compliance

Descriptive statistics will be used to summarize test article compliance for the Safety, PK, and evaluable populations. Measures of test article compliance will include the duration of treatment, the total number of applications (determined from the actual number of applications reported by the subject), and the percent of expected doses applied. A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of the expected number of applications prior to the HPA assessment. Subjects included in the PK analysis (PK population) must not have any significant protocol deviations, must have at least an 80% dose compliance based on number of applications, and must apply the final three doses as prescribed prior to the end of study PK assessment.

18.3.3.3 Safety Laboratory Tests

Laboratory data collected at Screening and Day 14 (or EOS), including clinical chemistry, hematology, and urinalysis, will be tabulated for each visit and changes from Screening to Day 14 (or EOS) will also be tabulated for the Safety population. All laboratory data will also be listed. Data will be reported in units received from the central laboratory. Shift tables by analyte and by out of range flag will also be presented to facilitate the evaluation of change from Screening at Day 14 (or EOS).

18.3.3.4 Local Skin Reactions

The frequency distributions of the severity of LSRs associated with the topical application of corticosteroids and/or acne including telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus will be summarized with frequency counts and percentages at Baseline, Day 7, and Day 14 for face and trunk, separately.

18.3.3.5 Adverse Events

All AEs reported during the study will be listed, documenting onset, whether therapy was required, any change in test article dosing, severity, possible relationship to test article, and outcome for the Safety population. Verbatim terms on the case report forms (CRFs) will be linked to preferred terms (PTs) and system organ class (SOC) using the MedDRA mapping system. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article.

18.3.3.6 Urine Pregnancy Tests

A listing of UPT results at Screening, Baseline, and Day 14 (or EOS) will also be prepared.

18.3.3.7 Physical Examination / Vital Signs

Physical examination findings at Screening and Day 14 will be recorded in medical history or as AEs. Vital signs will be recorded at Screening and Day 14.

18.3.3.8 Electrocardiogram

ECGs will be evaluated at Screening and Day 14 (or EOS) for any material changes.

18.4 Subgroup Analyses

No subgroup analyses are planned.

18.5 Interim Analyses

No interim analyses are planned.

19. ETHICAL AND REGULATORY CONSIDERATIONS

19.1 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 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/IEC 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.

19.2 Institutional Review Board / Ethics Committee and Informed Consent/Assent

Before study initiation, the investigator must have written and dated approval from the IRB/IEC 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/IEC with a copy of the product labeling, information to be provided to subjects and their parent/guardian and any updates. The investigator will submit documentation of the IRB/IEC approval to the CRO.

The IRB/IEC approved consent/assent form must include all elements required by FDA (or other Health Authority), 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 assent by signing and dating the approved informed 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.

19.3 Protocol Compliance

The IRB/IEC 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.

19.4 Protocol Revisions

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

New or altered consent/assent forms required by the IRB/IEC 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.

19.5 Study Monitoring

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

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

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

19.6 Case Report Form Requirements

The study will utilize validated 21CFR Part 11 compliant electronic data capture (EDC) software to collect data; all requested information must be entered on the eCRFs in the areas provided in a timely manner. When changes or corrections are made in the eCRF, 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 eCRF completion may make entries on the eCRFs. 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 eCRF. 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.

19.7 Reports to Institutional Review Board / Ethics Committee

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

19.8 Quality Assurance Audits

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

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

19.9 Records Retention

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

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

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

18.10 Record Confidentiality

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

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

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

20. REFERENCES

1. Cockcroft DW and Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. *Nephron* 16:31-41, 1976.

2. Celasco G, Moro L, Bozzella R, Ferraboshi P, Bartorelli L, Quattrochhi C, Nicoletti F. Biological profile of cortexolone 17α-propionate (CB-03-01), a new topical and peripherally selective androgen antagonist. *Arzneim Forsch* 54:881-6, 2004.

3. Study 171-7151-202. An Open Label Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Cortexolone 17α-Propionate (CB-03-01) Cream Applied Every Twelve Hours for Two Weeks in Subjects with Acne Vulgaris. Intrepid Therapeutics, 2014.

4. Method No. MN12059. Method for the Determination of Cortexolone-17-Alpha-Propionate and Cortexolone in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric Detection. MicroConstants, 2012.

5. Study No. PF12B-0163. Validation of a Method for the Determination of Cortexolone-17-Alpha-Propionate and Cortexolone in Human Plasma using High-Performance Liquid Chromatography with MS/MS Detection. MicroConstants, 2012.

APPENDIX 1 SAMPLE SUBJECT INSTRUCTION SHEET

Copies of the Subject Instruction Sheet will be provided to the study site. The investigator should provide this sheet to the subject and the subject's parent/guardian at Visit 2 / Baseline / Day 1. Any modifications to the sample provided must be approved by the IRB/IEC.

SAMPLE SUBJECT/PARENT 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 shown how and where to apply the study medication in the clinic.
- Wash the area to be treated (your face and trunk) with mild soap and water. Gently dry the area.
- Wash your hands before applying the study medication.
- Dispense 2 grams of study medication using the scale provided by the study doctor.
- Use the "Dab, Spread, Pat" method of application:
  - With one of your fingertips, DAB small amounts of the study medication onto all areas of your face (forehead, cheeks, nose, and chin), avoiding application on eyes.
  - SPREAD the study medication evenly with your fingertip to cover your entire face with a very thin even coat of the study medication.
  - Then, gently PAT the skin until the study medication has absorbed into the skin.
- Apply the remaining amount of the study medication to the areas of your trunk as instructed by the study staff using the "Dab, Spread, Pat" method until all of the study medication has been applied. This may include your shoulders, upper chest, and/or upper back (get assistance if you are not able to apply the study medication to your back on your own).
- Record date and time of study medication application in your subject diary.
- Wash your hands after applying the study medication.
- Do not wash the treated areas for at least 8 hours after application of the study medication.
- Do not cover or wrap areas where study medication was applied. Loose fitting clothing is recommended after application of study medication.
- Do not apply skin care products for at least 4 hours after application of the study medication.
- At home, apply the study medication every 12 hours as directed by the study doctor.

BEFORE EACH STUDY VISIT:

- Please shower or wash the areas to be treated before each clinic visit.
- **DO NOT APPLY THE STUDY MEDICATION ON THE DAY OF YOUR SCHEDULED STUDY VISITS.**

ADDITIONAL REMINDERS:

- Store the study medication 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 other children and pets.
- Discontinue use if skin irritation or rash develop and contact the study site.
- Do not swim or participate in any other activities which could potentially remove the product from the Treatment Area for the duration of the study

STUDY VISIT SCHEDULE:

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 at Visit 2 / Baseline / Day 1 and all follow-up visits as necessary.

SAMPLE SUBJECT DIARY for PROTOCOL CB-03-01/28

Apply the study medication as instructed by the study doctor. After dosing every 12 hours (each morning and evening), at approximately the same time each day, record the date and time that the dose was applied. ***If you miss a dose, write MISSED where the time is recorded.*** **PARENT/GUARDIAN SHOULD ASSIST IN RECORDING THE SUBJECT DIARY. DO NOT APPLY THE STUDY MEDICATION ON THE DAY OF YOUR SCHEDULED STUDY VISITS.**

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

Next appointment: _____, _____/_____/_____ at _____am
Week Day **dd MMM yy**

Return this diary, your used AND unused medication tubes at each visit.

If you have any questions,

Contact:_____ At:_____

Site Use Only:	
Subject #: ___ ___ ___	Initials: ___ ___ ___
Diary dispensed at:	Date Returned
Visit 2 (Day 1) ☐ Visit 3 (Day 7) ☐	

APPENDIX 3 TEST ARTICLE INFORMATION

A 3.1 Test Article Packaging and Labeling

The test articles will be packaged and labeled by Cassiopea S.p.A, Lainate Italy. CB-03-01 cream, 1% will be packaged in epoxy lined aluminum tubes, with a polypropylene cap closure, containing 30 grams of test article. Each subject will be assigned a subject number according to the numerical order that they will be enrolled in.

Over the duration of the study, the subjects will be dispensed the necessary amount of test article. Subjects should not have more than two tubes of test article in their possession at any one time. When the tubes are dispensed to subjects, the tube label should be completed entirely and the information documented on the Study Medication Accountability Log which is to be kept at the investigational site.

Tube labels will, at a minimum, contain the following information: protocol number, subject identifiers (subject number and initials to be filled in), an investigational test article disclaimer (e.g., Caution: New Drug, Limited by United States law to investigational use or similar language as appropriate for the Health Authority governing the site), and the appropriate storage conditions for the study medication.

A 3.2 Test Article Storage and Preparation

Study medication 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 tube labels.

A 3.3 Dispensing Test Article

Subjects who are eligible for enrollment in the study will be assigned a subject number. This number will consist of five digits, two digits for the site number, and three digits assigned 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 (or corresponding form of another Health Authority for sites in the EU) by authorized personnel as required by applicable regulations and guidelines.

On dispensing the test article for the first time at the Baseline Visit, each subject will be dispensed 2 tubes and the information will be recorded on the Study Medication Accountability Log. Each tube contains approximately 30 grams of test article and should last for approximately seven days with dosing every 12 hours.

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, the date of return and initials of

the individual accepting the return for each tube of test article will be documented on the same line of the Study Medication Accountability Log as the dispensing information.

At Visit 3 (Day 7), all tubes will be collected and weighed. The amount of test article applied (2 grams per application) should be verified by reviewing the drug weights and diary entries. Additional tubes may be dispensed for the next visit interval, as applicable. If necessary, review the application instructions with the subject.

At Visit 4 (Day 14 or EOS), all the tubes of test article that were dispensed to the subjects will be collected. Every effort should be made 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.

A 3.4 Test Article Supply Records at Study Sites

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

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

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

A 3.5 Dose Modifications

The subject should not modify the treatment regimen without consultation with the investigator. Subjects should be instructed to discontinue use if skin irritation or rash develop and 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 3.6 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). 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 3.7 Return and Destruction of Test Article Supplies

At completion or termination of the study, all unused and/or partially used test article tubes must be returned to the CRO, if not authorized by the CRO to be destroyed at the site. All tubes of the test article should 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 (0.1 gram) to document extent of subject exposure. Unless instructed otherwise by the Sponsor, the study site will keep the original Study Medication Accountability Log in the study file. A copy of the Study Medication Accountability Log will be returned to the Sponsor. All tubes of test article will then either be: a) returned to the study Sponsor, or b) provided to a sponsor-identified third party vendor for appropriate destruction according to applicable regulations with the provision of a certificate of destruction.

APPENDIX 4 COSYNTROPIN STIMULATION TEST PACKAGE INSERT

PRINTER TO INSERT BARCODE 3 OF 9

6959006F

FOR DIAGNOSTIC USE ONLY

CORTROSYN™

(cosyntropin) for Injection

DESCRIPTION

CORTROSYN™ (cosyntropin) for Injection is a sterile lyophilized powder in vials containing 0.25 mg of CORTROSYN™ and 10 mg of mannitol to be reconstituted with 1 mL of 0.9% Sodium Chloride Injection, USP. Administration is by intravenous or intramuscular injection. Cosyntropin is α 1 - 24 corticotropin, a synthetic subunit of ACTH. It is an open chain polypeptide containing, from the N terminus, the first 24 of the 39 amino acids of natural ACTH. The sequence of amino acids in the 1 - 24 compound is as follows:

Ser -	Tyr -	Ser -	Met -	Glu -	His -	Phe -	Arg -	Trp -	Gly -	Lys
1	2	3	4	5	6	7	8	9	10	11
Pro -	Val -	Gly -	Lys -	Lys -	Arg -	Arg -	Pro -	Val -	Lys -	Val
12	13	14	15	16	17	18	19	20	21	22
Tyr -	Pro									
23	24									

CLINICAL PHARMACOLOGY

CORTROSYN™ (cosyntropin) for Injection exhibits the full corticosteroidogenic activity of natural ACTH. Various studies have shown that the biologic activity of ACTH resides in the N-terminal portion of the molecule and that the 1 - 20 amino acid residue is the minimal sequence retaining full activity. Partial or complete loss of activity is noted with progressive shortening of the chain beyond 20 amino acid residues. For example, the decrement from 20 to 19 results in a 70% loss of potency.

The pharmacologic profile of CORTROSYN™ is similar to that of purified natural ACTH. It has been established that 0.25 mg of CORTROSYN™ will stimulate the adrenal cortex maximally and to the same extent as 25 units of natural ACTH. This dose of CORTROSYN™ will produce maximal secretion of 17-OH corticosteroids, 17- ketosteroids and / or 17 - ketogenic steroids.

The extra-adrenal effects which natural ACTH and CORTROSYN™ have in common include increased melanotropic activity, increased growth hormone secretion and an adipokinetic effect. These are considered to be without physiological or clinical significance.

Animal, human and synthetic ACTH (1-39) which all contain 39 amino acids exhibit similar immunologic activity. This activity resides in the C-terminal portion of the molecule and the 22-39 amino acid residues exhibit the greatest degree of antigenicity. In contrast, synthetic polypeptides containing 1-19 or fewer amino acids have no detectable immunologic activity. Those containing 1-26, 1-24 or 1-23 amino acids have very little immunologic although full biologic activity. This property of CORTROSYN™ assumes added importance in view of the known antigenicity of natural ACTH.

INDICATIONS AND USAGE

CORTROSYN™ (cosyntropin) for Injection is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency. Because of its rapid effect on the adrenal cortex it may be utilized to perform a 30-minute test of adrenal function (plasma cortisol response) as an office or outpatient procedure, using only 2 venipunctures (see DOSAGE AND ADMINISTRATION section).

Severe hypofunction of the pituitary - adrenal axis is usually associated with subnormal plasma cortisol values but a low basal level is not per se evidence of adrenal insufficiency and does not suffice to make the diagnosis. Many patients with proven insufficiency will have normal basal levels and will develop signs of insufficiency only when stressed. For this reason a criterion which should be used in establishing the diagnosis is the failure to respond to adequate corticotropin stimulation. When presumptive adrenal insufficiency is diagnosed by a subnormal CORTROSYN™ test, further studies are indicated to determine if it is primary or secondary.

Primary adrenal insufficiency (Addison's disease) is the result of an intrinsic disease process, such as tuberculosis within the gland. The production of adrenocortical hormones is deficient despite high ACTH levels (feedback mechanism). Secondary or relative insufficiency arises as the result of defective production of ACTH leading in turn to disuse atrophy of the adrenal cortex. It is commonly seen, for example, as result of corticosteroid therapy, Sheehan's syndrome and pituitary tumors or ablation.

The differentiation of both types is based on the premise that a primarily defective gland cannot be stimulated by ACTH whereas a secondarily defective gland is potentially functional and will respond to adequate stimulation with ACTH. Patients selected for further study as the result of a subnormal CORTROSYN™ test should be given a 3 or 4 day course of treatment with Repository Corticotropin Injection USP and then retested. Suggested doses are 40 USP units twice daily for 4 days or 60 USP units twice daily for 3 days. Under these conditions little or no increase in plasma cortisol levels will be seen in Addison's disease whereas higher or even normal levels will be seen in cases with secondary adrenal insufficiency.

CONTRAINDICATION

The only contraindication to CORTROSYN™ (cosyntropin) for Injection is a history of a previous adverse reaction to it.

PRECAUTIONS

General

CORTROSYN™ (cosyntropin) for Injection exhibits slight immunologic activity, does not contain animal protein and is therefore less risky to use than natural ACTH. Patients known to be sensitized to natural ACTH with markedly positive skin tests will, with few exceptions, react negatively when tested intradermally with CORTROSYN™. Most patients with a history of a previous hypersensitivity reaction to natural ACTH or a pre-existing allergic disease will tolerate CORTROSYN™. Despite this however, CORTROSYN™ is not completely devoid of immunologic activity and hypersensitivity reactions including rare anaphylaxis are possible. Therefore, the physician should be prepared, prior to injection, to treat any possible acute hypersensitivity reaction.

Drug Interactions

Corticotropin may accentuate the electrolyte loss associated with diuretic therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility. A study in rats noted inhibition of reproductive function like natural ACTH.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with CORTROSYN™ (cosyntropin) for Injection. It is also not known whether CORTROSYN™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. CORTROSYN™ should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CORTROSYN™ (cosyntropin) for Injection is administered to a nursing woman.

Pediatric Use

(See DOSAGE AND ADMINISTRATION section.)

ADVERSE REACTIONS

Since CORTROSYN™ (cosyntropin) for Injection is intended for diagnostic and not therapeutic use, adverse reactions other than a rare hypersensitivity reaction are not anticipated. A rare hypersensitivity reaction usually associated with a pre-existing allergic disease and/or a previous reaction to natural ACTH is possible. Symptoms may include slight whealing with splotchy erythema at the injection site. There have been rare reports of anaphylactic reaction. The following adverse reactions have been reported in patients after the administration of CORTROSYN™ and the association has been neither confirmed nor refuted:

- bradycardia
- tachycardia
- hypertension
- peripheral edema
- rash

DOSAGE AND ADMINISTRATION

CORTROSYN™ (cosyntropin) for Injection may be administered intramuscularly or as a direct intravenous injection when used as a rapid screening test of adrenal function. It may also be given as an intravenous infusion over a 4 to 8 hour period to provide a greater stimulus to the adrenal glands. Doses of CORTROSYN™ 0.25 to 0.75 mg have been used in clinical studies and a maximal response noted with the smallest dose.

A suggested method for a rapid screening test of adrenal function has been described by Wood and Associates (1). A control blood sample of 6 to 7 mL is collected in a heparinized tube. Reconstitute 0.25 mg of CORTROSYN™ with 1mL of 0.9% Sodium Chloride Injection, USP and inject intramuscularly. The reconstituted drug product should be inspected visually for particulate matter and discoloration prior to injection. Reconstituted CORTROSYN™ should not be retained. In the pediatric population, aged 2 years or less, a dose of 0.125 mg will often suffice. A second blood sample is collected exactly 30 minutes later. Both blood samples should be refrigerated until sent to the laboratory for determination of the plasma cortisol response by some appropriate method. If it is not possible to send them to the laboratory or perform the fluorimetric procedure within 12 hours, then the plasma should be separated and refrigerated or frozen according to need.

Two alternative methods of administration are intravenous injection and infusion. CORTROSYN™ can be injected intravenously in 2 to 5 mL of saline over a 2-minute period. When given as an intravenous infusion: CORTROSYN™, 0.25 mg may be added to glucose or saline solutions and given at the rate of approximately 40 micrograms per hour over a 6-hour period. It should not be added to blood or plasma as it is apt to be inactivated by enzymes. Adrenal response may be measured in the usual manner by determining urinary steroid excretion before and after treatment or by measuring plasma cortisol levels before and at the end of the infusion. The latter is preferable because the urinary steroid excretion does not always accurately reflect the adrenal or plasma cortisol response to ACTH.

The usual normal response in most cases is an approximate doubling of the basal level, provided that the basal level does not exceed the normal range. Patients receiving cortisone, hydrocortisone or spironolactone should omit their pre-test doses on the day selected for testing. Patients taking inadvertent doses of cortisone or hydrocortisone on the test day and patients taking spironolactone or women taking drugs which contain estrogen may exhibit abnormally high basal plasma cortisol levels.

A paradoxical response may be noted in the cortisone or hydrocortisone group as seen in a decrease in plasma cortisol values following a stimulating dose of CORTROSYN™.

In the spironolactone or estrogen group only a normal incremental response is to be expected. Many patients with normal adrenal function, however, do not respond to the expected degree so that the following criteria have been established to denote a normal response:

1. The control plasma cortisol level should exceed 5 micrograms/100 mL.
2. The 30-minute level should show an increment of at least 7 micrograms/100 mL above the basal level.
3. The 30-minute level should exceed 18 micrograms/100 mL. Comparable figures have been reported by Greig and co-workers (2).

Plasma cortisol levels usually peak about 45 to 60 minutes after an injection of CORTROSYN™ and some prefer the 60-minute interval for testing for this reason. While it is true that the 60-minute values are usually higher than the 30-minute values, the difference may not be significant enough in most cases to outweigh the disadvantage of a longer testing period. If the 60-minute test period is used, the criterion for a normal response is an approximate doubling of the basal plasma cortisol value.

In patients with a raised plasma bilirubin or in patients where the plasma contains free hemoglobin, falsely high fluorescence measurements will result. The test may be performed at any time during the day but because of the physiological diurnal variation of plasma cortisol the criteria listed by Wood cannot apply. It has been shown that basal plasma cortisol levels and the post CORTROSYN™ increment exhibit diurnal changes. However, the 30-minute plasma cortisol level remains unchanged throughout the day so that only this single criterion should be used (3).

Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit. Reconstituted CORTROSYN™ should not be retained.

HOW SUPPLIED

Box of 10 vials of CORTROSYN™ (cosyntropin) for Injection 0.25 mg

NDC # 0548-5900-00

Storage

Store at 15-30°C (59-86°F).

CORTROSYN™ is intended as a single dose injection and contains no antimicrobial preservative. Any unused portion should be discarded.

Rx only

REFERENCES

1. Wood, J.B. et al. LANCET 1.243, 1965.
2. Greig, W.R. et al. J. ENDOCR 34.411, 1966.
3. McGill, P.E. et al. ANN RHEUM DIS 26.123, 1967.

Amphastar Pharmaceuticals, Inc.
Rancho Cucamonga, CA 91730 U.S.A. REV. 9-05

APPENDIX 5 BODY MASS INDEX FOR AGE

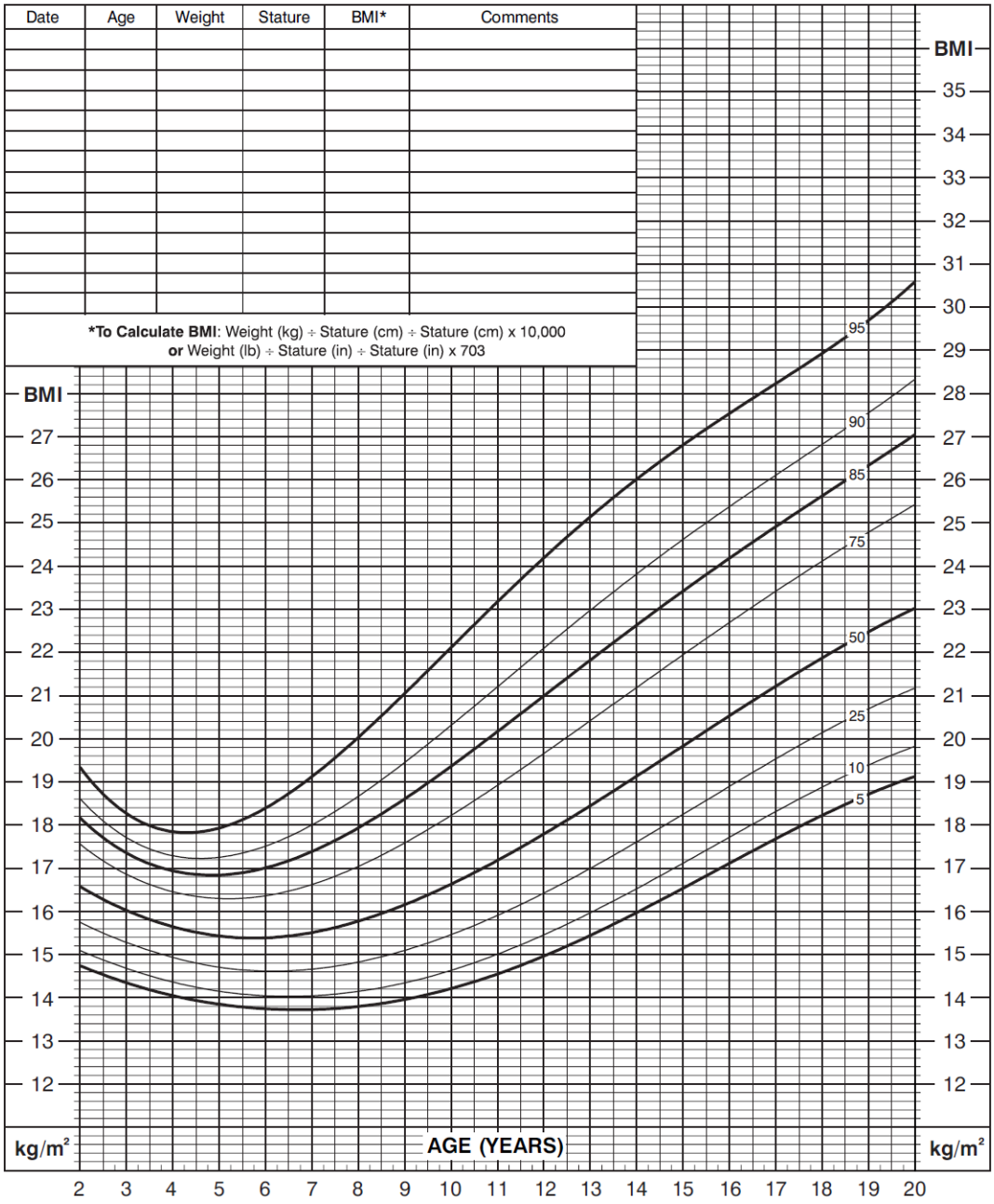
2 to 20 years: Boys
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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2 to 20 years: Girls
Body mass index-for-age percentiles

NAME _____

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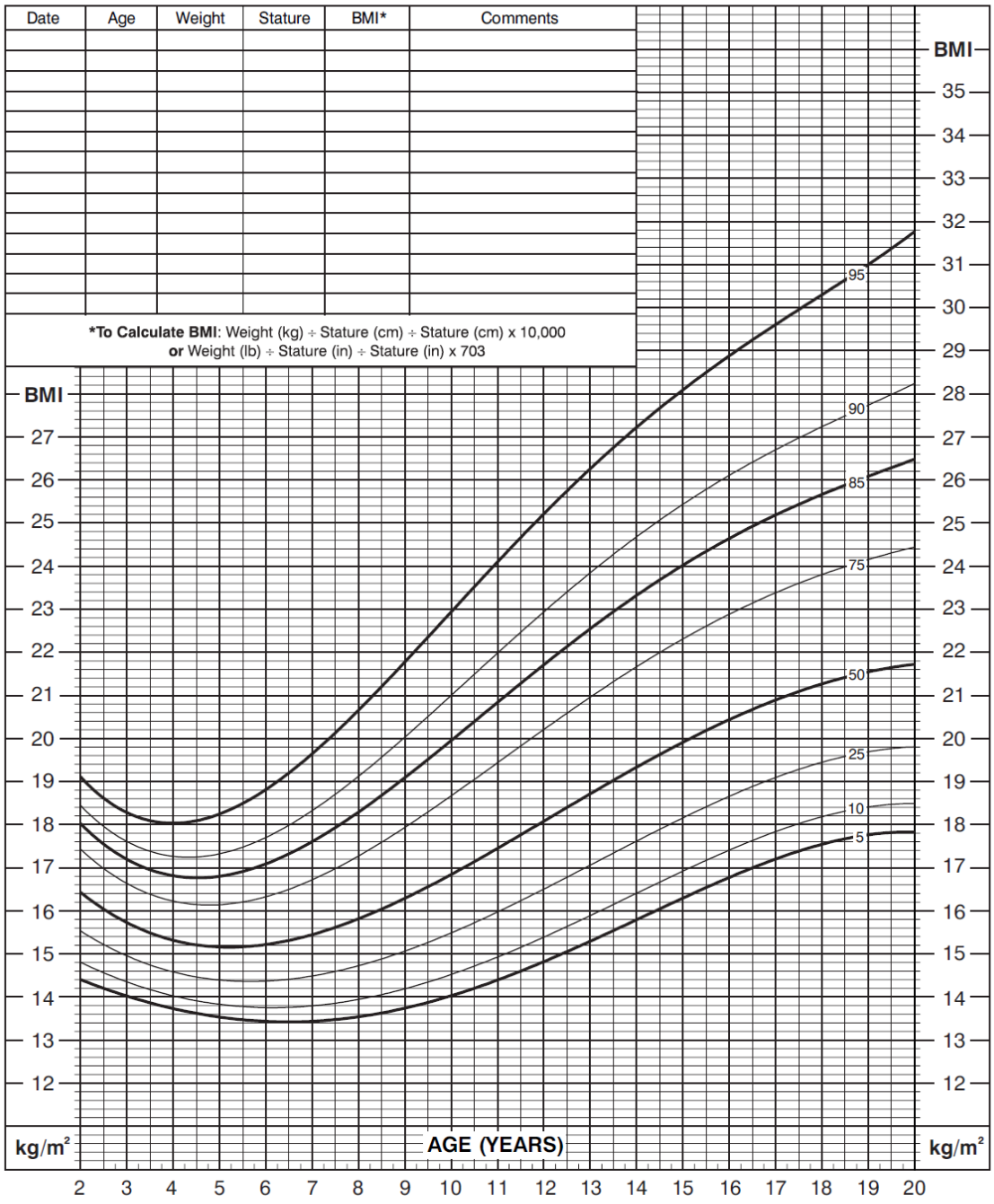
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



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