AN OPEN LABEL EVALUATION OF THE ADRENAL SUPPRESSION POTENTIAL AND PHARMACOKINETIC PROPERTIES OF TWICE DAILY HALOBETASOL PROPIONATE LOTION, 0.05% IN SUBJECTS 12 TO 16 YEARS 11 MONTHS OF AGE WITH PLAQUE PSORIASIS RECEIVING TWO WEEKS OF TREATMENT

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SPONSOR REPRESENTATIVE:	
MEDICAL MONITOR:	
PROJECT MANAGER:	

STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to Sun Pharmaceutical Industries, Inc. (hereafter referred to as Sun Pharma), the Sponsor.

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

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

I understand the study may be terminated or enrollment suspended at any time by Sun Pharma, 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 Sun Pharma and must be treated in the same manner as the contents of this protocol.

_____
Printed Name of Principal Investigator

_____ _____
Investigator Signature Date

Protocol number: 177-0551-201 Site number: ____

Version: 3.0

Date of final version: August 5, 2016

PROTOCOL SYNOPSIS

Title	An Open Label Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Twice Daily Halobetasol Propionate Lotion, 0.05% in Subjects 12 to 16 Years 11 Months of Age with Plaque Psoriasis Receiving Two Weeks of Treatment
Study Type	Phase 4
Test Article	Halobetasol propionate (HBP) Lotion, 0.05%
Study Objective	The objective of this study is to determine the adrenal suppression potential and the pharmacokinetic (PK) properties of HBP Lotion applied twice daily in subjects aged 12 to 16 years 11 months with stable plaque psoriasis.
Study Design	An open label, multicenter study.
Treatment Groups	All subjects will receive HBP Lotion, 0.05%.
Duration of Treatment	Up to two weeks.
Duration of Study	Participation in the study is a minimum of five weeks (at least 20 days between Screening and Baseline Visits, up to two weeks of treatment, and potential follow-up for any subjects who have evidence of hypothalamic-pituitary-adrenal [HPA] axis suppression).
Study Population	Male and female subjects aged 12 to 16 years 11 months with stable plaque psoriasis.
Total Number of Subjects	Subject enrollment will continue until at least 20 subjects with both Screening and End of Study (EOS) 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 25 subjects.
Number of Sites	Approximately four sites will participate in the study.
Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Subject is male or non-pregnant female 2. Subject has provided written informed assent and was accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian has provided informed consent for the subject. 3. Subject has a clinical diagnosis of stable plaque psoriasis involving a minimum of 10% body surface area (BSA)[1] within the Treatment Area.

[1] For this evaluation 1% BSA is approximately equivalent to the area of the subject's closed hand (palm and fingers held together).

	4. Subject has an Investigator's Global Assessment (IGA) score of at least three (3 = moderate) at the Baseline Visit. 5. Subject is willing and able to apply the test article as directed, comply with study instructions and commit to all follow-up visits for the duration of the study. 6. Females must have a negative urine pregnancy test (UPT)[2] at the Screening (Part B) and Baseline Visits and agree to use an effective form of birth control[3] for the duration of the study.
Exclusion Criteria	A subject is ineligible to enter the study if he/she meets one or more of the following criteria: 1. Subject has spontaneously improving or rapidly deteriorating plaque psoriasis. 2. Subject has guttate, pustular, erythrodermic or other non-plaque forms of psoriasis. 3. Subject has a physical condition which, in the investigator's opinion, might impair evaluation of plaque psoriasis, adrenal axis function (e.g., Addison's Disease, Cushing's Syndrome) or which exposes the subject to an unacceptable risk by study participation. 4. Subject has used any phototherapy (including laser), photo-chemotherapy or systemic psoriasis therapy including methotrexate, retinoids, cyclosporine or biologics within 30 days prior to the initiation of treatment with the test article. 5. Subject has used systemic corticosteroids (including oral or intramuscular) or topical, inhaled or intranasal corticosteroids within 30 or 14 days, respectively, prior to Part B of the Screening Visit and/or the subject has used systemic or topical corticosteroids between Part B of the Screening Visit and the initiation of treatment. 6. Subject has had prolonged exposure to natural or artificial sources of ultraviolet radiation within 30 days prior to the initiation of treatment or is intending to have such exposure during the study that is thought by the investigator to likely modify the subject's disease. 7. Subject has used topical psoriatic therapy including tar, anthralin, retinoids, vitamin D analogs (e.g., Dovonex®) within 14 days prior to the initiation of treatment with the test article. 8. Subject has used emollients/moisturizers on areas to be treated within one day prior to the initiation of treatment with the test article. 9. Subject is currently using lithium or Plaquenil (hydroxychloroquine). 10. Subject is currently using a beta-blocking medication (e.g., propranolol) or angiotensin converting enzyme (ACE) inhibitors (e.g., lisinopril) at a dose that has not been stabilized, in the opinion of the investigator.

[3] Effective forms of birth control include hormonal contraceptives [oral, injectable, transdermal or intravaginal] or intrauterine device (IUD) for two cycles (e.g., eight weeks) prior to test article application, condom and spermicidal or diaphragm and spermicidal). Other acceptable forms of birth control include: a) abstinence for subjects who are not sexually active or b) if the subject is in a monogamous relationship with a partner who is sterile (e.g., vasectomy performed at least six months prior to the subject's initiation of treatment). Subjects who become sexually active or begin to have relations with a partner who is not sterile during the trial must agree to use an effective form of birth control for the duration of the study.

	11. Subject has a history of sensitivity to any of the ingredients in the test article (see Section 6.1). 12. Subject is pregnant, lactating, or is planning to become pregnant during the study. 13. Subject is currently enrolled in an investigational drug or device study. 14. Subject has used an investigational drug or investigational device treatment within 30 days prior to Visit 1 (Screening). 15. Subject has been previously enrolled in this study and treated with the test article. 16. Subject has an irregular sleep schedule or works night shifts (cortisol levels exhibit physiological diurnal variation). 17. Subject has a screening Cosyntropin Stimulation Test (CST) with a post 30-minute stimulation cortisol level of ≤ 18 µg/dL. 18. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.
Study Procedures	The following procedures will take place according to the visit schedule: Visit 1 (Screening Visit) (-Day 20 or longer): At Visit 1 (Screening Visit), study procedures will be explained by the study coordinator and the 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 informed consent for the subject. Consent/assent must be signed prior to the initiation of any study-related procedures. At this visit, consenting/assenting subjects will have their medical history and Inclusion/Exclusion (I/E) criteria reviewed to determine subject eligibility. Subjects requiring a wash-out period will be asked to return to complete the following procedures of Screening Visit (Part B) once the wash-out is completed. All female subjects must have a negative UPT to be eligible for this study. Vital signs, height and weight, as well as IGA score, will be recorded. Subjects will have a Screening CST that should be initiated between 7 to 9AM to determine their adrenal system response. A Screening PK sample for drug concentration in plasma will be collected in all subjects in conjunction with the Screening CST. Enrollment into the treatment phase of the study (Baseline Visit) should be timed such that the Screening CST will be performed a minimum of 28 days before the projected end of the study phase. To accommodate this requirement, the Baseline Visit should ideally be scheduled at least 20 days after the Screening Visit. Visit 2 (Day 1/Baseline Visit): At Visit 2 (Day 1/Baseline Visit), subjects with a normal response to CST (post-stimulation serum cortisol > 18 µg/dL) and who continue to meet all the other I/E criteria will be enrolled in the study while subjects with significant abnormal screening results (particularly CST results; post-stimulation serum cortisol ≤ 18 µg/dL) will be discontinued as screen failures. All female subjects must have a negative UPT to continue in the study. A limited physical examination including vital signs and weight will be performed. IGA score will be recorded. Study staff will document percent BSA affected with disease and the percent BSA to be treated with the test article during the study at the Baseline Visit. Baseline local skin reactions (LSRs) will be recorded prior to test article application. All eligible subjects will apply the first dose in the clinic and be instructed

	to apply the assigned test article twice daily (approximately every 12 hours) to the psoriatic plaques designated by the investigator until Day 15. Each subject will be given a Subject Instruction Sheet and the study personnel will demonstrate how and where to dispense and apply test article to all the psoriatic plaques within the Treatment Area. The total dose of test article applied per week should be a maximum of approximately 50 grams/week. Any adverse events (AEs) or LSRs (i.e., burning/stinging only) post-application will be recorded. A Subject Diary will also be given to each subject with completion instructions. Visit 3 (Day 8 ± 1): Subjects will return to the clinic on Day 8 for the study staff to record IGA score, percent BSA affected, review test article compliance, and collect information on AEs and LSRs. Prior to the Day 8 visit, subjects will be requested to i) apply the test article at bedtime on Day 7 and record the time, then ii) withhold application of the test article on the morning of the visit (Day 8). All subjects, regardless of lesion clearance, will have blood drawn on the morning of Day 8 to assess drug concentrations in plasma (trough values - ~12 hours after previous dose). Any subject who has completely cleared their treated lesions (IGA score of 0 in Treatment Area) will discontinue dosing of test article, have a CST performed between 7 to 9AM, be assessed for any AEs and LSRs, review and document any concomitant medications, and complete EOS procedures on Day 8. If CST, AEs, LSRs, concomitant medications and EOS procedures cannot be performed on Day 8, then the subject will continue dosing of test article and return on Day 9 for CST and EOS procedures to be performed. Subjects who are clear at Day 8, complete CST on Day 8, and have all EOS procedures completed on Day 8 will exit the study at Day 8. Subjects who have not cleared by Day 8 will apply their morning dose at the clinic after the Day 8 trough blood sample is drawn and continue twice daily (approximately every 12 hours) application of the test article until Day 15. Their percent BSA to be treated will be documented at Day 8. Any AEs or LSRs (i.e., burning/stinging only) post-application will be recorded. Day 9 (Optional Visit): On the following day (Day 9), subjects cleared by Day 8 who could not have a CST and all EOS procedures performed on Day 8 will have blood taken as part of their EOS CST, be assessed for any AEs and LSRs, documentation of any concomitant medications and complete all EOS procedures at Day 9 and will exit the study. Visit 4 (Day 15 ± 2 or EOS): Subjects who have continued to apply test article through Day 14 will return to the clinic for the study staff to collect information on AEs, LSRs, draw a final trough PK blood sample prior (~12 hours following previous dose) to EOS CST, and perform the EOS CST. If any of these subjects have adrenal suppression (defined as post-CST cortisol level $\leq$ 18 µg/dL), they will be scheduled for one or more post-treatment follow-up visits. Study staff will document IGA score and percent BSA affected with disease. All female subjects will have urine pregnancy testing.

	Post-Treatment Follow-up Visits (Suppressed Subjects Only): Any subjects who have evidence of adrenal suppression at EOS will return approximately every four weeks BUT no sooner than four weeks (28 days) after the EOS visit, and subsequently approximately every four weeks BUT no earlier than every four weeks (>28 days) thereafter for CST until the adrenal response returns to normal. Subjects with other ongoing AEs that require follow-up may also be followed per the discretion of the investigator.
Study Measurements	The following assessments will be performed: Investigator's Global Assessment: At Screening, Baseline Visit/Day 1, Day 8, and Day 15/EOS, the overall severity of the subject's psoriasis in the Treatment Area will be evaluated using the IGA score (5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe). The IGA score is a static evaluation of the overall or "average" degree of severity taking into account all of the subject's psoriatic lesions in the Treatment Area (excluding those on the face, scalp, groin, axillae and other intertriginous areas) by the investigator or designee. This evaluation takes into consideration the three individual characteristics of psoriasis (scaling, erythema and plaque elevation) with the IGA score at each visit representing the average of scaling, erythema or plaque elevation that is present amongst all of the lesions eligible for treatment. Percent BSA Affected with Disease: This is defined as the BSA which is affected with psoriasis within the Treatment Area. The percent BSA affected with psoriasis will be estimated at the Baseline Visit/Day 1, Day 8, and Day 15/EOS. Percent BSA Treated with Test Article: This is defined as the BSA which is affected with psoriasis within the Treatment Area that will be treated. The percent BSA to be treated with the test article will be estimated at Baseline and Day 8. Test Article Compliance: Subjects will apply the first dose of test article to all plaques within the Treatment Area under staff supervision. At each visit, subject diaries will be reviewed to determine test article doses taken since the last visit and subjects will be counseled regarding compliance if necessary. Subjects will be instructed to record the date that the last dose was applied. All dispensed bottles of test article will be weighed at each visit and the amount of test article used will be recorded.

	Local Skin Reactions: At each visit, subjects will be evaluated for the presence of any LSRs associated with the topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, and folliculitis. Adverse Events: All AEs will be recorded. At each visit after the Baseline Visit, subjects will also be questioned specifically about the status of any ongoing AEs. Pharmacokinetic Assessment: Eligible subjects will have blood drawn at Screening for baseline drug concentration in plasma. On Day 8, all subjects, regardless of lesion clearance, will have blood drawn for assessment of trough drug concentration in plasma. At the Day 15 visit, subjects who have continued to treat lesions will have a final assessment of trough drug concentration in plasma approximately 12 hours after their Day 14 evening application and just prior to the initiation of the CST.
Study Endpoints	HPA Axis Response to Cosyntropin - Measurement of serum cortisol concentrations after stimulation of the adrenal cortex with cosyntropin (Cortrosyn® tests). HPA axis suppression is defined as a post-stimulation serum cortisol level $\leq$ 18 µg/dL assessed at the end of study. Plasma Levels of HBP - Trough HBP concentrations in plasma will be assessed at Screening, Day 8 and Day 15/EOS approximately 12 hour post-treatment. Other Safety Endpoints - AEs, LSRs, UPTs, dosing compliance, and extent of exposure.
Sample Size Calculations	No formal power calculations were performed to establish the sample size. The number of subjects enrolled who complete the study is historically consistent with other HPA studies.
Statistical Methods	All statistical analyses and summaries will be prepared using SAS® unless otherwise stated. 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. All enrolled subjects who applied at least one dose of test article and returned for at least one post-baseline visit will be considered the modified intent-to-treat (mITT) population.

	Safety Analyses: Dosing Compliance Descriptive statistics will be used to summarize test article compliance for the mITT and the PK populations. Measures of test article compliance will include the duration of treatment (number of days dosed), 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% but no more than 120% of the expected number of applications. Extent of Exposure The total amount of test article used (grams of test article applied) will be calculated from the weights of the returned test articles. Descriptive statistics (mean, median, standard deviation [SD], minimum and maximum) will be determined for the total amount of test article used by each subject in the mITT and PK populations. Urine Pregnancy Tests A listing of UPT results will also be prepared. Local Skin Reactions The frequency distributions of the severities of LSRs associated with topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, and folliculitis will be summarized at Baseline and all follow-up visits. Adverse Events All subjects enrolled in the study who were dispensed and applied test article at least once will be included in the safety analyses (Safety population). 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. Verbatim terms on the case report forms (CRFs) will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) mapping system. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article. HPA Axis Suppression Analysis HPA axis responses to CST will be dichotomized to normal and abnormal. The mean increases in serum cortisol levels after stimulation will also be summarized at the end of study. In addition, descriptive statistics for the daily dose of test article will be tabulated separately for suppressed and non-suppressed subjects. Post-treatment follow up data will be summarized for subjects determined to have laboratory based evidence of adrenal suppression at the end of study or early termination visit.

	Pharmacokinetic Analysis Trough HBP concentrations in plasma on Day 8 and Day 15 will be calculated and summarized.

SCHEDULE OF EVENTS

Study Day	*Visit 1 Screening[1] (-Day 20 or longer)*	*Visit 2 Day 1 Baseline*	*Visit 3 Day 8 (± 1)*	*Optional Visit Day 9*	*Visit 4 EOS Day 15[2,3] (± 2) or Early Term*
Informed Consent/Assent	X				
Medical History, Demographics, Vital Signs, Height and Weight	X	Reconfirm (except height)			
Limited Physical Exam		X			
Inclusion/Exclusion Criteria	X	Reconfirm			
Urine Pregnancy Test (UPT)[4]	X	X	X[5]	X[5]	X
Cortrosyn® Stimulation Test (CST)	X[6]	Confirm eligibility[6]	X[7]	X[7]	X[7]
Percent BSA Affected with Disease	Confirm eligibility	X	X		X
Investigator's Global Assessment (IGA) Score	X	X	X	X[5]	X[5]
Percent BSA to be Treated with Test Article	Confirm eligibility	X	X		
Provide (or review) Instruction Sheet to Subject and Demonstrate How to Apply the Test Article		X	X		
Provide Subject Diary to Subject and Completion Instructions		X	X		
Study Treatment (approximately every 12 hours)		X	X[5] (withhold AM application until after trough PK blood draw)		
Concomitant Medication Assessments	X	X	X	X[5]	X
Adverse Events Assessment	X	X	X	X[5]	X

Study Day	*Visit 1 Screening[1] (-Day 20 or longer)*	*Visit 2 Day 1 Baseline*	*Visit 3 Day 8 (± 1)*	*Optional Visit Day 9*	*Visit 4 EOS Day 15[2,3] (± 2) or Early Term*
Record Local Skin Reactions		X (pre- and post-test article application)[9]	X (pre- and post-test article application)[8]	X[5]	X
Drug Accountability (with Weights)		X	X	X[5]	X[9]
PK Blood Draws	X		X (trough approx. 12 hours post-treatment on Day 7)	X[5] (trough approx. 12 hours post-treatment on Day 8)	X (trough approx. 12 hours post-treatment; Pre-CST)

1 To be performed 20 or more days prior to the Baseline visit (Day 1).
2 If results at Final Visit show evidence of adrenal suppression, testing will be performed at 4-week intervals until adrenal axis function has normalized or stabilized.
3 Final scheduled visit occurs at Day 15 $\pm$ 2.
4 All female subjects will have a UPT at Screening, Baseline and at the end of study
5 Subjects with an IGA score of 0 (clear) for their treated lesions on Day 8 will discontinue topical application of the test article, have all EOS procedures performed (or on Day 9 if morning PK, CST and other EOS procedures cannot be done on Day 8), and will exit the study at this visit. The last application of test article for those who have cleared and are completing the study on Day 8 will be on the evening of Day 7, for those subjects who have cleared and are completing the study on Day 9 the last application will be on the evening of Day 8.
6 Subjects with an abnormal CST at Screening will be discontinued from the study.
7 Subjects who have cleared their treated lesions by Day 8 (IGA score of 0) will have a CST performed on Day 8 (7AM to 9AM) and not on Day 15 with the option of having CST performed 7AM to 9AM on Day 9 if CST cannot be done on Day 8.
8 All LSRs will be assessed pre-application and only burning/stinging will be assessed post-application.
9 Weigh and collect test articles at the end of study visit.

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AUCτ	Area Under the Curve at Steady-State
β-hCG	Beta-human Chorionic Gonadotropin
b.i.d.	Twice a day
BSA	Body Surface Area
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Peak Concentration
CRF	Case Report Form
CST	Cosyntropin Stimulation Test
dL	Deciliter
EDC	Electronic Data Capture
EOS	End of Study
FDA	Food and Drug Administration
HBP	Halobetasol Propionate
HDPE	High Density Polyethylene
HPA	Hypothalamic-Pituitary-Adrenal
I/E	Inclusion/Exclusion
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine Device
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mIU	Milli-International Units
mL	Milliliters
µg	Micrograms
oz	ounce
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Standard Deviation
SOC	System Organ Class
TI	Therapeutics, Incorporated
T_{max}	Time to Peak Concentration
UPT	Urine Pregnancy Test

USP	United States Pharmacopeia
VCA	Vasoconstrictor Assay
WHO	World Health Organization

TABLE OF CONTENTS

1. BACKGROUND

Halobetasol propionate (HBP) is a well-known corticosteroid with anti-inflammatory properties. It is indicated for the local topical treatment of various inflammatory skin disorders (e.g., psoriasis). At present, there are three topical formulations of halobetasol propionate (Ultravate®) on the market – one is an ointment formulation, one is a cream formulation, and one is a lotion formulation, each containing 0.05% halobetasol propionate. Based on vasoconstrictor assay (VCA) studies, these formulations have been designated as Class I super-high potency corticosteroids **(1)**.

Systemic activity of topical corticosteroids depends on their absorption, metabolism, distribution, elimination and potency. The extent of the absorption of topically applied corticosteroids is dependent on structure and concentration of the corticosteroid, the vehicle used, duration and frequency of application, occlusion, condition of the skin and individual variation.

Determination of plasma or serum cortisol concentrations before, during and after application of topical corticosteroid-containing formulations provides an indication of a suppression of the production of cortisol and provides more information than measurement of cortisol metabolites in urine. Measurement of plasma or serum cortisol concentrations after stimulation of the adrenal cortex with cosyntropin (Cortrosyn®) tests the ability of the HPA axis to react as a negative feedback mechanism **(2, 3)**. Such "laboratory-based" adrenal suppression with different ointment and cream formulations containing 0.05% halobetasol propionate respectively, after one week of twice daily treatment, has been previously reported **(4)**. More recently, a study was conducted to determine and compare the adrenal suppression potential and the pharmacokinetic (PK) properties of HBP Lotion, 0.05% versus Ultravate® Cream applied twice daily in adult subjects with moderate to severe psoriasis **(5)**. Results of this study support the safety of HBP Lotion, 0.05% with respect to adrenal suppressive effects and systemic exposure in adults with moderate to severe plaque psoriasis treated twice daily for up to two weeks. Of the 42 intent-to-treat subjects considered evaluable, only three (14.3%) Ultravate® Cream-treated subjects and five (23.8%) HBP Lotion-treated subjects demonstrated an abnormal HPA-Axis response at end of treatment. PK data from a subgroup of 24 subjects demonstrated systemic exposure to HBP from both treatments was similar as determined from peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), and area under the curve over a dosing internal (AUC_{τ}) at steady-state.

2. RATIONALE

Adrenal suppression effects of topical corticosteroids, especially super-high potency or Class I corticosteroids, are among the most important safety concerns for this group of products. This study is designed to determine the adrenal effects of the investigational lotion formulation of halobetasol propionate, 0.05% and characterize the steady-state

pharmacokinetics of the investigational lotion formulation in male and female subjects aged 12 to 16 years 11 months with stable plaque psoriasis.

3. OBJECTIVE

The objective of this study is to determine the adrenal suppression potential and the PK properties of an investigational lotion formulation of halobetasol propionate, 0.05% (HBP Lotion) applied twice daily in subjects aged 12 to 16 years 11 months with stable plaque psoriasis.

4. STUDY DESIGN

This is an open label, multicenter study of an investigational formulation of HBP Lotion, 0.05% in male and female subjects aged 12 to 16 years 11 months with stable plaque psoriasis. Approximately 25 subjects with stable plaque psoriasis on at least 10% of their BSA (excluding the face, scalp, groin, axillae and other intertriginous areas), who fulfill the inclusion/exclusion criteria will be enrolled at multiple study sites. All subjects will have a screening CST to assess their HPA axis response at Visit 1 (Screening Visit). Enrollment into the treatment phase of the study should be timed such that the screening CST will be performed a minimum of 20 days before Baseline Visit. At Visit 2 (Baseline), eligible subjects with normal adrenal function will be eligible to participate in the study.

Subjects will apply HBP Lotion, 0.05% to all psoriasis plaques identified at Visit 2 twice daily (approximately every 12 hours) for the assigned treatment period or until the investigator verifies the subject's psoriasis has cleared. The study is designed to determine the adrenal suppression potential and pharmacokinetic properties of the test article after the subject applies a maximum of approximately 50 grams per week for up to a two week treatment period. All subjects will have a CST to reassess their HPA axis response at EOS (or earlier if the investigator verifies the subject's psoriasis has cleared). In this study, an abnormal HPA axis response to 0.25 milligram dose of cosyntropin is defined as a post-CST serum total cortisol level of $\leq$ 18 µg/dL.

5. STUDY POPULATION

5.1 Subject Eligibility

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

5.1.1 Inclusion Criteria

1. Subject is male or non-pregnant female
2. Subject has provided written informed assent and was accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian has provided informed consent for the subject.
3. Subject has a clinical diagnosis of stable plaque psoriasis involving a minimum of 10% BSA
4. Subject has an Investigator's Global Assessment (IGA) score of at least three (3 = moderate) at the Baseline Visit.
5. Subject is willing and able to apply the test article as directed, comply with study instructions and commit to all follow-up visits for the duration of the study.
6. Females must have a negative urine pregnancy test (UPT)[5] at the Screening (Part B) and Baseline Visits and agree to use an effective form of birth control[6] for the duration of the study.

5.1.2 Exclusion Criteria

1. Subject has spontaneously improving or rapidly deteriorating plaque psoriasis.
2. Subject has guttate, pustular, erythrodermic or other non-plaque forms of psoriasis.
3. Subject has a physical condition which, in the investigator's opinion, might impair evaluation of plaque psoriasis, adrenal axis function (e.g., Addison's Disease, Cushing's Syndrome) or which exposes the subject to an unacceptable risk by study participation.
4. Subject has used any phototherapy (including laser), photo-chemotherapy or systemic psoriasis therapy including methotrexate, retinoids, cyclosporine or biologics within 30 days prior to the initiation of treatment with the test article.
5. Subject has used systemic corticosteroids (including oral or intramuscular) or topical, inhaled or intranasal corticosteroids within 30 or 14 days, respectively, prior to Part B of the Screening Visit and/or the subject has used systemic or topical corticosteroids between Part B of the Screening Visit and the initiation of treatment.
6. Subject has had prolonged exposure to natural or artificial sources of ultraviolet radiation within 30 days prior to the initiation of treatment or is intending to have such

[6] Effective forms of birth control include hormonal contraceptives [oral, injectable, transdermal or intravaginal] or intrauterine device (IUD) for two cycles (e.g., eight weeks) prior to test article application, condom and spermicidal or diaphragm and spermicidal). Other acceptable forms of birth control include: a) abstinence for subjects who are not sexually active or b) if the subject is in a monogamous relationship with a partner who is sterile (e.g., vasectomy performed at least six months prior to the subject's initiation of treatment). Subjects who become sexually active or begin to have relations with a partner who is not sterile during the trial must agree to use an effective form of birth control for the duration of the study.

exposure during the study that is thought by the investigator to likely modify the subject's disease.
7. Subject has used topical psoriatic therapy including tar, anthralin, retinoids, vitamin D analogs (e.g., Dovonex®) within 14 days prior to the initiation of treatment with the test article.
8. Subject has used emollients/moisturizers on areas to be treated within one day prior to the initiation of treatment with the test article.
9. Subject is currently using lithium or Plaquenil (hydroxychloroquine).
10. Subject is currently using a beta-blocking medication (e.g., propranolol) or angiotensin converting enzyme (ACE) inhibitors (e.g., lisinopril) at a dose that has not been stabilized, in the opinion of the investigator.
11. Subject has a history of sensitivity to any of the ingredients in the test article (see Section 6.1).
12. Subject is pregnant, lactating, or is planning to become pregnant during the study.
13. Subject is currently enrolled in an investigational drug or device study.
14. Subject has used an investigational drug or investigational device treatment within 30 days prior to Visit 1 (Screening).
15. Subject has been previously enrolled in this study and treated with the test article.
16. Subject has an irregular sleep schedule or works night shifts (cortisol levels exhibit physiological diurnal variation).
17. Subject has a screening Cosyntropin Stimulation Test (CST) with a post 30-minute stimulation cortisol level of ≤ 18 µg/dL.
18. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.

5.1.3 Subject Withdrawal Criteria

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

Halobetasol Propionate Lotion, 0.05% (HBP Lotion)
Active ingredient: Halobetasol propionate
Other ingredients:

6.2 Instructions for Use and Application

Subjects will apply a maximum of approximately 50 grams weekly of the HBP Lotion to affected areas designated by the investigator, twice daily (approximately every 12 hours) for up to two weeks. Subjects will be provided with an instruction sheet (refer to Appendix 1) which includes detailed instructions for the application of test article.

6.2.1 Test Article Application

A study staff member will demonstrate how to dispense the test article and instruct the subject on the proper application of the test article to the affected areas at the Baseline Visit.

All eligible subjects will apply the first dose in the clinic and be instructed to apply the assigned test article twice daily to the psoriatic plaques designated by the investigator until Day 15 or until the investigator verifies their psoriasis has cleared, whichever comes first.

Subjects should be instructed to wash their hands before and after each test article application. Instructions are as follows:

The subject will be provided with instructions on how to apply the test article (see Appendix 1). The test article should be spread uniformly to cover the psoriatic lesions designated by the investigator within the Treatment Area.

Subjects should apply the test article twice a day (approximately 12 hours apart) to all

As the subject's plaques improve or worsen the amount of test article applied will likely decrease or increase, respectively.

If the subject's disease is too extensive to be reasonably managed with the approximately 50 grams per week limitation, then the subject should not be enrolled in the study or should be discontinued from the study. Lesions not treated with test article may be managed with emollient as detailed below. If the subject's disease becomes unmanageable because of these limitations, he/she should be discontinued from the study.

At Day 8, all subjects will return to the clinic for the study staff to record percent BSA affected, record percent BSA treated, IGA, review test article compliance, and collect information on AEs and LSRs. All subjects, regardless of lesion clearance, will have blood drawn on the morning of Day 8 to assess drug concentrations in plasma (trough values). Any subject who has completely cleared their treated lesions (IGA score of 0 in Treatment Area) will discontinue dosing of test article, have a CST performed between 7 and 9AM, be assessed for any AEs and LSRs, review and document any concomitant medications, and complete EOS procedures on Day 8. If CST, AEs, LSRs, concomitant medications and EOS procedures cannot be performed on Day 8, then the subject will continue dosing of test article and return on Day 9 for morning PK, CST and all EOS procedures to be performed. Subjects who are clear at Day 8, complete CST on Day 8, and have all EOS procedures completed on Day 8 will exit the study at Day 8.

Subjects who have not cleared by Day 8 will apply their morning dose at the clinic after the Day 8 trough blood sample is drawn and continue twice-daily application of the test article until Day 15. Their percent BSA affected and percent BSA treated will be

documented at Day 8. Any AEs or LSRs (i.e., burning/stinging only) post-application will be recorded.

Subjects will apply their final dose on the evening of Day 14 and record the time of the application. The final application of test article on Day 14 should be approximately 12 hours before the final PK blood is drawn on the morning of Day 15.

At Day 15, subjects who have continued to apply test article through Day 14 will return to the clinic for the study staff to collect information on AEs and LSRs, record percent BSA affected, draw a final trough PK blood sample prior to EOS CST, and perform the EOS CST. All units of test article will be collected and weighed. If any of these subjects have adrenal suppression they will be scheduled for one or more post-treatment follow-up visits.

6.2.2 Treatment Duration

The subject will apply the test article to all psoriasis plaques identified at Visit 2 (Baseline) in the Treatment Area, including any new lesions identified by the investigator that may develop in this area during the study, twice daily for two weeks or until the investigator verifies the subject's psoriasis has cleared (see Section 10.3 for management of subjects that may clear prior to Day 15).

6.2.3 Dose Modifications

The subject should not modify the treatment regimen without consultation with the investigator. 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 Study Medication Compliance Form.

6.2.4 Documentation of Compliance

A Study Medication Compliance Form will be used to report the frequency of test article applications for each subject. The date of the first application of test article will be recorded on the CRFs. Any changes from the twice daily application specified in the protocol (e.g., missed applications, investigator directed reduction in application frequency) will also be recorded. The date of the last application of the test article will be recorded on the End of Study CRF.

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

6.3 Warnings, Precautions and Contraindications

The test article is for topical use only. Care should be taken to avoid contact with eyes and all mucous membranes. If contact with eyes occurs, rinse thoroughly with water. Do not apply to face, scalp, groin, axillae and other intertriginous areas.

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, discontinue use.

Subjects should not occlude the treated areas.

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

The effects of HBP Lotion, 0.05% in nursing mothers, pregnant women and their unborn children are unknown. Women of childbearing potential must not be pregnant or planning a pregnancy during the study period.

7. SUBJECT NUMBER ASSIGNMENT

Subjects who consent to participate in the study and meet the inclusion/exclusion criteria will be assigned a subject "screening" number at Visit 1. The screening number will consist of the two digit site number (e.g., "02-" in the following example) and an ascending two digit number, beginning with 01 that identifies the specific subject (for example, 02-01, 02-02, etc.). This screening number will be used on the screening laboratory requisition forms and screening laboratory test results.

Subjects who complete the screening phase of the study and are eligible for enrollment into the treatment phase of the study will be assigned a three digit (starting at 101 for Site 01, 201 for Site 02, 301 for Site 03, etc.) subject number at Visit 2 (Baseline). Assignment of a subject number at each site will start with the lowest unassigned subject number assigned to a site and progress in sequential order.

8. PRIOR AND CONCOMITANT THERAPIES

Current medications and any medications taken in the 45 days prior to Visit 1 (Screening) will be recorded as prior/concomitant medications with the corresponding indication. The medications to be recorded include prescription and over-the-counter medications (except vitamins and dietary supplements). All medications taken on a regular basis should be recorded on the CRFs prior to commencing the use of the test article.

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Vitamins and mineral supplements are permitted at dosages considered by the investigator

as reasonable for maintaining good health. Non-prohibited chronic therapies being used at Visit 1 may be continued. Any changes in concomitant therapies during the study must be recorded on the CRFs. The reason for any change 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.

8.1 Prohibited Medications or Therapies

Include medications within the following categories:

- Topical or systemic medications intended to treat psoriasis including but not limited to those listed in Section 5.1.2 (e.g., retinoids, vitamin D analogs, anthralin, cyclosporine, and biologics).
- Steroids – Systemic or topically administered, including inhaled or nasally administered treatments or ophthalmic preparations. This includes OTC topical steroid products (e.g., products containing 0.5% or 1% hydrocortisone).

8.2 Allowed Medications or Therapies

Subjects may use an investigator-approved, medicated (non-steroid) shampoo to treat scalp psoriasis and the bland emollient to treat areas of psoriasis that are not treated with the test article. In the event that a bland emollient is used that is different than the product supplied by the Sponsor, the investigator must approve the use of this moisturizer to assure it meets protocol requirements as a bland moisturizer.

For subjects who demonstrate adrenal suppression at the end of study, therapies that will not affect their adrenal function (e.g., topical tazarotene, emollients, etc.) may be used to treat their plaque psoriasis during the follow-up evaluation.

All concomitant therapies, including the standard emollient and the investigator-approved shampoo must be recorded on the CRFs. All concomitant medications will be coded with the current version of the WHO Drug Dictionary.

9. STUDY PROCEDURES

9.1 Study Flow Chart

10. VISIT ACTIVITIES

Specific activities for each study visit are listed below.

10.1 Visit 1 – Screening Visit (-Day 20 or Longer)

This visit should be scheduled between 7 and 8AM given the timing requirements for the study and the CST should be performed a minimum of 20 days before the Baseline Visit.

PART A

At this visit, the investigator or designee will:

- Obtain a signed, written informed assent from the subject. The subject must 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. Consent/assent must be signed prior to the initiation of any study-related procedures.
- Assign each eligible subject a "screening" number.
- Complete the Medical History and Demographics Form.
- Review current medications and therapies.
- Confirm the subject meets the inclusion/exclusion criteria.
- Have the subject complete washout from any prohibited medications, if necessary. This may require that the subject return to the clinic to complete the remaining visit procedures.
- Schedule the Visit for Part B; ideally at least 20 days prior to the Baseline (Day 1) Visit.

PART B

NOTE: Part B activities can be done concurrently with Part A if no washout period is required but should occur a minimum of 20 days prior to the Baseline (Day 1) Visit.

At this visit, the investigator or designee will:

- Perform a UPT for all female subjects; the results must be negative for the subject to participate in Part B of the screening phase.
- Record changes to current concomitant medications and therapies.
- Reconfirm the subject meets the inclusion/exclusion criteria.
- Record vital signs, height and weight.
- Record IGA score.
- Perform a CST, see Section 13.1. CST should be initiated between 7 and 9AM at this visit. If the CST cannot be initiated before 9AM, another visit should be scheduled to complete Part B.

- Draw blood for Baseline drug concentration in plasma.
- Inform the subject that if the serum cortisol levels or CST results are not within the normal range, he/she will not be eligible for the study.
- Schedule Visit 2 (Day 1/Baseline Visit). This visit should ideally be scheduled at least 20 days after completion of Visit 1, Part B.
- Update the Subject Screening and Enrollment Log.

10.2 Visit 2 (Day 1) Baseline

Prior to Visit 2, the investigator will review the subject's Visit 1 CST results. Any subject with abnormal HPA axis function (see Section 13.1) will be considered a "screen failure" and will be discontinued from the screening phase of the study following the procedures in Section 14.3. Only subjects who meet all of the eligibility criteria (Sections 5.1.1 and 5.1.2) will be assigned a subject number for the treatment phase of the study.

At this visit, the investigator or designee will:

- Reconfirm medical history and demographics.
- Perform a limited physical examination including vital signs and weight.
- Reconfirm the subject meets the eligibility criteria, including CST results. Subjects must meet all the inclusion criteria and none of the exclusion criteria to be enrolled in the study.
- Perform a UPT for all female subjects; the results must be negative for the subject to be enrolled.
- Record any changes (including new medications) to current concomitant medications and therapies.
- Record IGA score.
- Document the percent BSA affected with disease.
- Record the location and percent BSA of the plaques to be treated with the test article on a body diagram in the subject's instruction sheet.
- Query subject about the presence of any burning/stinging in the Treatment Area and examine them for the presence of any telangiectasia, skin atrophy, or folliculitis in the Treatment Area prior to test article application for Baseline assessment.
- If the subject still meets the eligibility criteria, assign the subject the next available (lowest) subject number in ascending order.
- Update the Subject Screening and Enrollment Log.
- Dispense the initial and back-up units of test article as described in Appendix 3 (Section A3.3).
- Dispense standard (bland) emollient as required.

NOTE: Standard (bland) emollient is to be used only on non-diseased skin or diseased skin not being treated with the test article as outlined in Section 6.2.1. Other

emollients should be avoided during the trial except with the approval of the investigator to assure they are a bland emollient.

- Instruct the subject how and where to apply the initial dose of test article following the procedures in Section 6 and in Appendix 1. The first dose of test article will be applied in the clinic.
- Document the percent BSA treated with test article.
- Instruct the subject to apply the second dose of test article in the evening of the visit day and continue twice daily applications of the test article as instructed (see Section 6) to all psoriasis plaques identified within the Treatment Area identified at this visit.
- Query subject about the presence of any burning/stinging in the Treatment Area post-application of the test article.
- Identify an investigator-approved, medicated (non-steroid) shampoo the subject will use for treating scalp psoriasis only, if appropriate.
- Dispense the Subject Instruction Sheet (Appendix 1) and the Subject Diary (Appendix 2) to the subject and provide instructions regarding how to complete the diary.
- Remind the subject to record the time of the last application of test article in the Subject Diary the evening before (Day 7) the Visit 3 (Day 8) clinic visit and to NOT apply any test article on the morning of the Visit 3 (Day 8) clinic visit.
- Schedule Visit 3 (Day 8 ± 1) – The timing of this visit should occur so that the trough PK blood draw on Day 8 occurs approximately 12 hours post-treatment on Day 7.

10.3 Visit 3 (Day 8 ± 1)

For Visit 3 (Day 8 ± 1), the specific procedures performed will depend on whether the psoriatic lesions within the Treatment Area are completely clear or not.* Subjects will be requested to withhold application of the test article on the morning of the visit until after the trough PK blood draw has been taken.

***NOTE:** The site may want to schedule all subjects between 7 to 8AM or call the subject the day before the visit to see if their Visit 3 appointment needs to be adjusted to the earlier time window because it appears their disease may have cleared.

At this visit, the investigator or designee will:

- Observe/query the subject about any changes in his/her health since the previous study visit and specifically about LSRs associated with topical application of the test article (see Section 12). Initiate/update the appropriate adverse event form as required.
- Review the subject's compliance with the study requirements.

- Query the subject about any changes in concomitant therapies (including the standard emollient and the investigator-approved medicated shampoo as appropriate) since the previous study visit and document the findings.
- Record IGA score. A subject's plaque psoriasis is defined as cleared if the investigator reports a grade of 0 for IGA per Section 11 of the protocol.
- Document the percent BSA affected with disease.
- Withhold AM application of test article until after trough PK blood draw.
- Draw blood to assess drug concentration in plasma (trough value).
- For subjects that have cleared completely:[7]
    - Perform CST between 7 to 9AM as per Section 13.1 and complete the End of Study Form unless their CST test reveals adrenal suppression. If a subject has an abnormal HPA axis function, report as an adverse event and follow the subject approximately every four weeks as described in Sections 10.6 and 13.1.1.
    - Perform a UPT for all female subjects.
    - Collect the Subject Diary and update the subject's Study Medication Compliance Form CRF with dates of missed doses, if applicable.
    - Collect and weigh all units of test article and record the final weights in the CRF. No further treatment will be applied.[8]
- For subjects that have not cleared:
    - Document the percent BSA to be treated with test article
    - Apply the AM dose at the clinic after the trough PK blood draw.
    - Collect used test article after the morning application (including weights) and re-dispense test article as necessary.
    - Instruct subjects to continue twice daily application and diary activities through the evening of the day prior (Day 14) to the next clinic visit (Day 15) and remind the subject:
        1) to record the time of the last application of test article in the Subject Diary the evening before (Day 14) the Visit 4 (Day 15) clinic visit and,
        2) to NOT apply any test article on the morning of the Visit 4 (Day 15) clinic visit.
    - Query subject about the presence of any burning/stinging in the Treatment Area post-application of the test article.
    - Schedule Visit 4 (Day 15 ± 2) – The timing of this visit should occur so that the trough PK blood draw on Day 15 occurs approximately 12 hours post-treatment on Day 14.

[7] For subjects clear at Day 8, the end of study procedures may be done the following day on Day 9 if they cannot be completed on Day 8.
[8] If the subject has to return on Day 9 to complete end of study procedures then the subject will continue to dose on Day 8 (AM & PM dosing). The Day 9 visit must occur the day immediately after the Day 8 visit.

- Schedule the end of study visit (Day 15) for the morning so that the CST will occur at the same time (± one hour) as the CST performed at Visit 1 (Screening). If possible, the CST should be initiated between 7 and 9AM.

10.4 Day 9 (Optional Visit)

Subjects who cleared by Day 8 and could not have a CST and all EOS procedures performed on Day 8 will continue application of test article that evening and return the following day (Day 9) to have blood taken as part of their trough PK and EOS CST, be assessed for any AEs, documentation of any concomitant medications and complete all EOS procedures. These subjects will then exit the study at this visit.

10.5 Visit 4 (Day 15 ± 2) or End of Study

These activities may occur as scheduled at the end of the assigned treatment period (15 days) or earlier for subjects if the investigator verifies the subject's psoriasis has cleared as defined per protocol (Visit 3, Day 8).

This visit should occur so that the CST is initiated at approximately the same time (± one hour) as the CST performed at Visit 1 (Screening).

At this visit, the investigator or designee will:

- Observe/query the subject about any changes in his/her health since the previous study visit and specifically about LSRs associated with topical application of the test article (see Section 12). Initiate/update the appropriate adverse event form as required.
- Review the subject's compliance with the study requirements.
- Query the subject about any changes in concomitant therapies (including the standard emollient and the investigator-approved medicated shampoo as appropriate) since the previous study visit and document the findings.
- Document the percent BSA affected with disease.
- Record IGA score.
- Perform a UPT for all female subjects.
- Collect the final blood sample for drug concentration in plasma just prior to the initiation of the CST.
- Perform a CST (see Section 13.1).
- After review of serum cortisol levels, complete the End of Study Form, unless the subject has an abnormal HPA axis response, then follow the procedures in Section 13.1.1.
- Collect and weigh all units of test article and record the final weights in the CRF.

If the end of study period CST results show a subject has an abnormal HPA axis function, report as an adverse event and follow the subject approximately every four (4) weeks as described in Sections 10.6 and 13.1.1.

10.6 Post-Treatment Follow-Up Visits – Suppressed Subjects Only

These visits are only required for subjects who have demonstrated abnormal CST consistent with suppression at the end of study and are returning for the follow-up CST as per Section 13.1.1. Subjects with other ongoing AEs that require follow-up may also be followed per the discretion of the investigator.

At this visit, the investigator or designee will:

- Observe/query the subject about any changes in his/her health since the previous study visit. Initiate/update the appropriate adverse event form as required.
- Query the subject about any changes in concomitant therapies (including the standard emollient and the investigator-approved medicated shampoo as appropriate) since the previous study visit and document the findings. Ensure that any concomitant medications are not prohibited (see Section 8.1).
- Perform the CST. This test should be initiated at approximately the same time (± one hour) as the CST performed at Screening and if possible, the CST should be initiated between 7 and 9AM (see Section 13.1).
- Complete the End of Study Form after review of the serum cortisol levels unless the subject has an abnormal HPA axis response, then follow the procedures in Sections 13.1 and 13.1.1.
- Notify the subject if he/she needs to return to the clinic if the result is abnormal. Repeat CST will be performed approximately every four (4) weeks until adrenal axis function has been documented to return to normal.

11. CLINICAL EVALUATIONS

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

11.1 Investigator's Global Assessment

The IGA score (5-point scale of 0 to 4) is an evaluation of the overall severity of a subject's psoriasis in the Treatment Area and takes into consideration the three individual characteristics of psoriasis (scaling, erythema and plaque elevation).

The investigator should NOT refer to any other assessments to assist with this evaluation. This evaluation is NOT a comparison with the IGA at any other visit. The test article should not be applied within eight (8) hours prior to the scheduled clinic visit. At Screening, Baseline Visit/Day 1, Day 8, and Day 15/EOS, the investigator will evaluate all active psoriasis plaques that are in the Treatment Area and report the single integer score that describes the overall severity of the subject's psoriasis using the following scale:

11.2 Percent Body Surface Area Affected with Disease

This is defined as the BSA which is affected with psoriasis within the Treatment Area.

he percent BSA affected with psoriasis will be estimated at the Baseline Visit/Day 1, Day 8, and Day 15/EOS. The investigator may use the estimate that 1% BSA is equivalent to the area of the subject's closed hand (palm with fingers held together).

11.3 Percent Body Surface Area Treated with Test Article

This is defined as the BSA which is affected with psoriasis within the Treatment Area that will be treated.

The percent BSA to be treated will be estimated at Baseline and Day 8.

11.4 Photography

Photography documentation is not required in this study. However, during the study, the investigator may photograph areas of diseased skin of the subject per his/her discretion for informational purposes only (e.g., documentation of adverse event, etc.). These photographs will not be used for grading or any other similar study-related purpose.

12. LOCAL SKIN REACTIONS ASSOCIATED WITH TOPICAL APPLICATION OF CORTICOSTEROIDS

At all post-screening visits, the investigator or designee will observe or directly query the subject regarding local skin reactions known to be associated with topical application of corticosteroids. The severity of the following local skin reactions: telangiectasia, skin atrophy, burning/stinging and folliculitis will be recorded as none, mild, moderate, or severe. A LSR is to be recorded as an adverse event only if therapy or discontinuation of test article is required.

13. LABORATORY TESTS

13.1 Cosyntropin Stimulation Test

At Visit 1 (Screening Visit, Part B), a cosyntropin stimulation test will be initiated for each subject between 7 and 9AM.

At the End of Study visit (i.e., the visit at which psoriasis has cleared or end of the assigned treatment period), a CST (and any follow-up CSTs) should be ideally initiated between 7 and 9AM but within ± one hour of the screening CST, after confirmation that the subject has not applied test article at least 8 hours prior to the visit.[9] If these conditions are not met, the subject should be rescheduled for CST on the next day.

Perform the cosyntropin stimulation test as follows:

- Collect a pre-stimulation blood sample (approximately 6-7 mL) as specified in the Laboratory Manual.
- Reconstitute one vial of cosyntropin (0.25 milligrams) in sodium chloride for injection USP (the volume of sodium chloride in the package insert for Cortrosyn [Appendix 4] is 2 to 5 mL).
- Inject the cosyntropin intravenously (the length of time during which the cosyntropin should be injected is 2 minutes [Appendix 4]).
- Thirty minutes after completing the cosyntropin injection collect a post-stimulation blood sample (approximately 6-7 mL) as specified in the Laboratory Manual.

If the results of the Visit 1 (Screening) CST indicate the subject has an abnormal HPA axis response the subject should be classified as a screen failure and withdrawn from the study following the procedures in Section 14.3. 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 end of study CST results show an abnormal HPA axis response the test article will be considered to have caused adrenal suppression in the subject. Report this abnormality (ACTH stimulation test abnormal) 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 plaque psoriasis. The subject should be scheduled to return for a follow-up visit no less than four (4) weeks after the end of study laboratory samples are collected (see Section 13.1.1). 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

[9] Site may wish to contact subject a day or so prior to the scheduled visit to confirm visit time and remind subject not to apply test article within eight (8) hours of the scheduled visit, and the subject should be fasting for approximately 8 hours prior to the visit.

normal. During this time, the subject may continue to use the standard emollient and the investigator-approved, medicated (non-steroid) shampoo as well as topical psoriatic therapy as recommended by the investigator which do not contain steroids. Systemic corticosteroids are also not permitted during this time.

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:

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

13.1.1 Post-Treatment Follow-Up (only if suppressed at the End of Study)

These visits should continue approximately every four (4) weeks (no less than every 28 days) until the subject's HPA axis response has returned to normal or other satisfactory resolution is documented. These visits should occur such that the CST is performed at the same time (± one hour) as the CST performed at Visit 1 (Screening, Part B) and if possible, ideally the CST should be initiated between 7 and 9AM. The specific procedures performed at these visits are detailed in Section 10.6.

13.2 Pregnancy Tests

UPTs will be performed at the study site if the site meets local country requirements to perform the testing (e.g., United States sites registered and conforms to Clinical Laboratory Improvement Amendments (CLIA) regulations for such testing [site possesses at a minimum a current valid CLIA Certificate of Waiver]) or at an appropriately registered reference laboratory. A UPT will be performed on all female subjects (Section 10.1) at Visit 1 (prior to CST), Visit 2 (prior to treatment) and at the end of study or if the subject withdraws prematurely. The investigator will report the UPT results on the CRFs, in the subject's medical records and in any independent records maintained at the study site. The urine pregnancy test used must have a minimum sensitivity of 25mIU of β-hCG/mL of urine.

13.3 Pharmacokinetic Tests

Blood (approximately 5 mL) for PK analysis will be drawn three times: at Screening (pre-application, time=0) and at Day 8 and Day 15 (unless IGA=0 at Day 8), approximately 12 hours after the dose on the previous day. All eligible subjects will have blood drawn at Screening for baseline drug concentration in plasma. On Day 8, all subjects, regardless of lesion clearance, will have blood drawn for assessment of trough drug concentration in plasma. Prior to the visit, subjects will be reminded to record i) the 12-hour "clock" time that the test article was applied in the evening of the day before the visit (Day 7) and ii) withhold application of the morning dose of test article on the morning of the visit (Day 8) until after the trough PK blood draw has been taken. Following this trough PK blood draw, subjects will apply, under supervision from the study staff, the morning dose of test article to the designated area and the time of application will be recorded and the percent BSA treated with test article and percent BSA affected will be recorded. Subjects who have cleared their treated lesions by Day 8 will not apply the Day 8 morning dose (unless CST and EOS procedures need to be performed on Day 9). At the Day 15 visit, subjects who have continued to treat lesions will have a final PK blood sample collected approximately 12 hours after their Day 14 evening application and just prior to the initiation of the CST.

All blood samples will be processed, stored and transported per the methodology provided by the analytical laboratory.

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

Subjects who complete the treatment as specified in the protocol and who complete the End of Study evaluations will be considered to 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 and/or parent/guardian decide it is in the subject's best interest to withdraw. NOTE: if the subject and/or parent/guardian decide it is in the subject's best interest to withdraw due to an AE then it should be classified as withdrawal due to an AE.
- Whenever the investigator decides it is in the subject's best interest to be withdrawn
- AEs
- Worsening of condition or treatment failure (in the opinion of the investigator)
- Intercurrent illness which may, in the investigator's opinion, significantly affect assessment of clinical status

- Noncompliance
- Pregnancy
- Lost to follow-up
- Sponsor administrative reasons

14.3 Screen Failures

If a subject is a screen failure due to Visit 1 laboratory results that show an abnormal pre-CST serum cortisol level or abnormal HPA axis function (a low post-CST serum cortisol level), complete the Screen Failure CRF. No clinical evaluation or follow-up CST will be performed in these subjects; however, the laboratory results will be provided to the subject's parent with a recommendation to follow up with the subject's regular healthcare provider.

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 assessment.

Subject enrollment will continue until at least 20 subjects with both Screening and End of Study 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 25 subjects.

14.4 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 working days.

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

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 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; where in such cases, the event should be recorded as an adverse event and reported to the Institutional Review Board (IRB) as an "unanticipated problem" in accordance with local procedures. Other changes in subject health information becomes AE data when the subject begins dosing with the test article and therefore AE data should be collected from the date of the first dose of test article. These data are considered treatment-emergent AEs.

Timely and complete reporting of all AEs assists Therapeutics, Inc. (TI) 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

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

The investigator will instruct the subject to report any adverse events 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 adverse event is transient and easily tolerated by the subject.

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

Severe - The adverse event 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 adverse event 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 adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

An adverse event 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 adverse events 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.

Adverse skin reactions have been reported with the use of topical corticosteroids and may occur more frequently with high potency corticosteroids such as halobetasol cream and ointment. These reactions include stinging, burning, itching, erythema, acne, dry skin, folliculitis, leukoderma, telangiectasia, pustulation, hypertrichosis, acneiform eruptions,

hypopigmentation, perioral dermatitis, allergic contact dermatitis, vesicles, rash, paresthesia, urticaria, secondary infection, skin atrophy, striae and miliaria. **(4, 5, 6)**.

Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia and glucosuria in some patients. In rare instances, treatment (or withdrawal of treatment) of psoriasis with corticosteroids is thought to have provoked the pustular form of the disease **(6)**.

Risks associated with venipuncture and the CST are listed in Section 13.1.

15.2 Serious Adverse Event

An event that is serious must be recorded on the AE CRF and on the Therapeutics, Inc. SAE Report Form, and requires expeditious handling to comply with regulatory requirements. SAEs will also be reported by TI to the Sponsor's pharmacovigilance team.

An adverse event 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 adverse events 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.

Adverse events classified as "serious" by either the investigator or the Sponsor require expeditious handling and reporting to TI 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.

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 TI, if available.

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

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

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

15.3 Pregnancy

All female subjects must agree to use an effective form of birth control during the course of the study[10] in a manner such that risk of failure is minimized. Prior to study enrollment,

[10] Effective forms of birth control include hormonal contraceptives [oral, injectable, transdermal or intravaginal] or IUD for two cycles (e.g., eight weeks) prior to test article application, condom and spermicidal or diaphragm and spermicidal). Other acceptable forms of birth control include: a) abstinence for subjects who are not sexually active or b) if the subject is in a monogamous relationship with a partner who is sterile (e.g., vasectomy performed at least six months prior to the subject's initiation of treatment). Subjects who become sexually active or begin to have relations with a partner who is not sterile during the trial must agree to use an effective form of birth control for the duration of the study.

all female subjects must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

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

All female subjects enrolling into the study must have a pregnancy test, prior to study therapy, if specified in the protocol. The study therapy must be withheld until the results of laboratory pregnancy testing are known. If pregnancy is confirmed during screening, the subject must not receive investigational product and must not be enrolled in the study.

If a subject or investigator suspects that a subject may be pregnant at any time during the study the investigational product must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or apply further investigational product 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 investigational product 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 TI. The investigator must notify the IRB of any pregnancy associated with the study therapy and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated, including counseling of the subject by the investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the investigator must report to TI, on the appropriate TI 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 adverse event, any complications during pregnancy should be recorded as AEs (or SAEs – if they fulfill the SAE criteria). Abortion, whether accidental, therapeutic or spontaneous should be reported as a SAE. Offspring should be followed for a minimum of eight weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to test article should be recorded as a SAE and details documented in the pregnancy surveillance form.

16. BLINDING/UNBLINDING

This is an open label study and all subjects will apply HBP Lotion, 0.05%.

17. CLINICAL SUPPLIES

17.1 Test Article Information

HBP Lotion, 0.05% will be purchased by the Sponsor or designee. Detailed information on the packaging/labeling, storage and preparation, dispensing and accountability are included in Appendix 3.

17.2 Supplies Provided by Therapeutics, Inc.

- CRFs
- Template source documents
- Site Regulatory Binder
- Standard bland emollient
- Cosyntropin (Cortrosyn®)
- UPT kits
- Weighing scales (if necessary)
- Timers

17.3 Supplies Provided by Investigator

- Primary urine collection containers

17.4 Supplies Provided by the Clinical Laboratory

- Supplies to collect and transport urine and blood samples to the clinical laboratory

18. STATISTICAL CONSIDERATIONS

18.1 Sample Size

Subject enrollment will continue until at least 20 subjects with both Screening and EOS serum cortisol data (pre- and post-cosyntropin stimulation) have completed the study without any significant protocol deviations (evaluable subjects). This may require the enrollment of approximately 25 subjects.

No formal power calculations were performed to establish the sample size. The number of subjects enrolled who complete the study is historically consistent with other HPA studies.

18.2 Endpoints

18.2.1 Efficacy Endpoints

The primary objective of this study is to assess safety, not efficacy. However, IGA and percent BSA treated and affected with disease will be assessed to document any changes

that are observed with regard to IGA and percent BSA. Descriptive statistics will be provided for any changes from Baseline in IGA and percent BSA.

18.2.2 Safety Endpoints

HPA Axis Response to Cosyntropin
HPA axis responses to stimulation by cosyntropin will be dichotomized to "normal" and "abnormal". An abnormal HPA axis response is defined as a 30-minute post-stimulation serum cortisol level that is ≤18 µg/dL at the end of study.

Plasma Levels of HBP
Trough HBP concentrations in plasma on Day 8 and Day 15 will be calculated and summarized.

Other Safety Endpoints
Other safety endpoints will include AEs, LSRs associated with topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, and folliculitis, UPTs, dosing compliance, and extent of exposure.

18.3 Statistical Methods

All statistical analyses and summaries will be prepared using SAS® unless otherwise stated. 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 will apply the initial dose of test article in the clinic on Day 1. All enrolled subjects who applied at least one dose of test article and returned for at least one post-baseline visit will be included in the modified ITT (mITT) population. Subjects discontinued from the study at Visit 2 due to abnormal screening laboratory test results or other ineligibility criteria (screen failures) will be excluded from the HPA axis suppression summaries. Subjects included in the pharmacokinetic analysis (PK population) must not have any significant protocol deviations and must have at least an 80% - 120% dose compliance based on number of applications. Clinical study sites should make every effort so that subjects do not miss consecutive doses.

Demographic and baseline characteristics (including the percent BSA affected and the percent BSA treated) will be summarized for the mITT, Safety 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, SD, median, minimum and maximum will be reported for the continuous variables.

Frequency counts and percentages for IGA scores at each visit and descriptive statistics (sample size, mean, SD, median, minimum and maximum) will be summarized for the percent BSA affected and the percent BSA treated with the test article at each visit.

18.3.1 Safety Analyses

Dosing Compliance
Descriptive statistics will be used to summarize test article compliance for the mITT and PK populations. Measures of test article compliance will include the duration of treatment (number of days dosed), 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% but no more than 120% of the expected number of applications.

Extent of Exposure
The total amount of test article used (grams of test article applied) will be calculated from the weights of the returned test articles. Descriptive statistics (mean, median, SD, minimum and maximum) will be determined for the total amount of test article used by each subject in the mITT and PK populations.

An approximation of the amount of test article applied per cm^2 prior to the collection of PK samples will be determined at Visit 3 from the estimate of the percent BSA treated with the test article. The BSA treated with test article (in square centimeters) will be determined from the Mosteller calculation **(7)**. The amount of test article applied will be determined by weighing the bottle before and after the dose of test article is applied on the morning of Day 8.

Urine Pregnancy Tests
A listing of UPT results will also be prepared.

Local Skin Reactions
The frequency distributions of the severities of LSRs associated with topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, and folliculitis will be summarized at Baseline and all follow-up visits.

Adverse Events
All subjects enrolled in the study who were dispensed and applied test article at least once will be included in the safety analysis (Safety population). 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. Verbatim terms on the CRFs will be linked to PTs and 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.

18.3.2 HPA Axis Suppression Analyses

The proportion of subjects manifesting adrenal suppression at the end of study (as defined in Section 18.2.2) will be summarized. The mean increases in serum cortisol levels after stimulation will also be summarized at the end of study. In addition, descriptive statistics

for the daily dose of test article will be tabulated separately for suppressed and non-suppressed subjects. Post-treatment follow up data will be summarized for subjects determined to have laboratory based evidence of adrenal suppression at the end of study or early termination visit.

18.3.3 Pharmacokinetic Analyses

Trough HBP concentrations in plasma on Day 8 and Day 15 will be calculated and summarized.

18.4 Subgroup Analyses

No subgroup analyses will be performed.

18.5 Interim Analyses

No interim analyses will be performed.

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 approval prior to study initiation. Voluntary informed consent will be given by every subject's parent/guardian prior to the initiation of any study-related procedures. Subjects must provide written assent. 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 and Informed Consent/Assent

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent/assent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects and their parent/guardian. The investigator should also provide the IRB 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 approval to Therapeutics, Inc.

The IRB-approved consent/assent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

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

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

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

19.5 Study Monitoring

Representatives of Therapeutics, Inc. 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 Therapeutics, Inc. 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 CRF data. All requested information must be entered on the CRFs in the areas provided in a timely manner. When changes or corrections are made in the CRF,

the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change and the reason for the change. Only individuals listed on the Delegation of Responsibilities Log with responsibility for CRF completion may make entries on the CRFs. Usernames and passwords will be provided to each authorized user to allow access to the training module. Access to additional features and functions will not be enabled until the user has successfully completed the training.

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

19.7 Reports to Institutional Review Board

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

19.8 Quality Assurance Audits

Representatives from Therapeutics, Inc. and/or the Sponsor or a third party selected by the Sponsor may conduct a quality assurance 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 TI in the event of a FDA site audit.

19.9 Records Retention

The investigator must maintain all study records (including test article disposition, informed consents, CRFs/data clarification forms, source documents, correspondence, regulatory documents, contracts, etc.) for a period of at least two years following the date of a marketing approval for the drug for the indication for which it is being investigated; or if no application is filed or if the application is not approved for such an indication, until two years after the investigation is discontinued and the FDA is notified.

The investigator must contact Therapeutics, Inc. 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 Therapeutics, Inc.

Therapeutics, Inc. will notify the investigator/Institution in writing when the related records are no longer needed.

19.10 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 guardian, except as necessary for monitoring by Therapeutics, Inc. or the Sponsor, the FDA or other regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study shall not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Therapeutics, Inc. or the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

20. REFERENCES

1. Stoughton RB. Vasoconstrictor assay--specific applications. In: Maibach HI, Surber C. eds. *Topical Corticosteroids*. Basel: Karger; 1992: 42-53.

2. Cortrosyn® (cosyntropin) for Injection (Package Insert). Rancho Cucamonga, California: Amphastar Pharmaceuticals, Inc.: 2010.

3. Evaluation of Endocrine Function in Clinical and Diagnosis Management by Laboratory Methods. John Bernard Henry, 18th Edition, W.B. Saunders Company, 1991. p. 331.

4. Ultravate® Cream and Ointment (Package Insert). Ranbaxy, Jacksonville, Florida; August 2012.

5. 000-0551-202 A Comparative Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Twice Daily Halobetasol Propionate Lotion 0.05% versus Halobetasol Propionate Cream 0.05% in Subjects with Moderate to Severe Plaque Psoriasis Receiving Two Weeks of Treatment. Therapeutics, Inc., 2011.

6. Investigator Brochure, Halobetasol Propionate Lotion, 0.05%; Edition 9.0. August 5, 2016.

7. Mosteller RD. Simplified calculation of body-surface area. *New Eng. J. Med*. 1987; 317, 1098.

APPENDIX 1 SAMPLE SUBJECT INSTRUCTION SHEET

A copy of the Subject Instruction Sheet will be provided to each study site. This sample instruction sheet may be used or modified by the investigator. If the instruction sheet is modified (other than the addition of "contact" information), the Subject Instruction Sheet will need to be reviewed by the Sponsor and approved by the governing IRB prior to use.

The investigator should provide a copy of the instruction sheet to each subject at the Baseline Visit.

NOTE: Subjects should be scheduled to arrive at the office approximately one hour before the scheduled time for the blood draw for serum cortisol. This will help to ensure that the serum cortisol data will be evaluable.

The Visit 1 CST should be initiated between 7 and 9AM. For each subject, any follow-up CST (Visit 4 or at the end of study) should be initiated at approximately the same time as the Visit 1 CST was performed (± one hour).

Visit 3 should be scheduled at the lower end of the visit window (e.g., Day 8 should be scheduled on Day 7 or 8). This will allow the scheduling of a "next" day visit (if necessary to perform the CST) within the visit window.

To remain within the designated visit windows, it may be necessary to schedule Saturday clinic visits.

SAMPLE SUBJECT INSTRUCTION SHEET FOR PROTOCOL 177-0551-201

Please follow these instructions carefully. Contact the study staff at the telephone number noted below if you have any questions about the study:

Contact:_____ At:_____

BACK OF INSTRUCTION SHEET

STUDY VISIT SCHEDULE:

VISIT 2: Date: Time:	VISIT 3: Date: Time:
VISIT 4: Date: Time:	

NOTE: Additional visits may be required at 4-week intervals (no less than every 28 days) if your laboratory test is abnormal after Visit 4.

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 the Baseline Visit (Visit 2/Day 1) and Visit 3 (Day 8) if all the affected areas of psoriasis are not completely clear.

SAMPLE SUBJECT DIARY for PROTOCOL 177-0551-201

APPENDIX 3 TEST ARTICLE INFORMATION

A 3.1 Test Article Packaging and Labeling

HBP Lotion, 0.05% will be purchased by the Sponsor or designee.

Test Article Labeling
HBP Lotion, 0.05% will be labeled, at a minimum, with the following information:

- Protocol No.: 177-0551-201
- Site / Subject number: (to be filled in, XX/XXX)
- Bottle unit number
- Contents: Halobetasol Propionate Lotion, 0.05%
- Storage statement

A 3.2 Test Article Storage and Preparation

The test article should be stored at the site between 15° C and 30° C (59° F and 86° F) in a secure area according to local regulations.

A 3.3 Dispensing Test Article

The study staff should assign the subject numbers in ascending order beginning with the lowest available subject number.

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

When dispensing the test article, record the site/subject number, bottle unit number(s), date dispensed and dispenser's initials for each bottle of test article dispensed on the Investigational Test Article Accountability Log provided. Record the weight of each dispensed bottle to the nearest tenth gram (0.1 gram).

On dispensing the test article for the first time (Visit 2/Day 1) provide each subject with two bottles (Bottle Units #1 and #2) and record the above information on the Investigational Test Article Accountability Log. The second bottle (Bottle Unit #2) of test article will be used in the event of loss, spillage or damage to the first bottle. A single bottle contains approximately 60 grams of test article and should last for one week and maintain compliance with the dosing regimen (maximum of approximately 50 grams per week).

The subject will also be instructed to bring all the test articles provided to each clinic visit.

At Visit 3 (Day 8) dispense a new bottle of test article (Bottle Unit #3). The subject should be instructed to use the second bottle and keep the third as the back-up.

When the subject returns each used bottle of test article, record the date of return and initials of the individual accepting the return for each bottle of test article on the same line of the Investigational Test Article Accountability Log as the dispensing information. Make every effort to obtain the return of all dispensed bottles of test article. Record the weights of all returned bottles on the Test Article Accountability Log. If these efforts fail, make a detailed note of the reason for the failure in the source documents and on the Comments page of the CRFs.

A 3.4 Test Article Supply Records at Study Sites

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

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

TI 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. 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 Study Medication Compliance Form in the subject's CRFs.

A 3.6 Documentation of Application and Compliance

A Study Medication Compliance Form will be used to report the frequency of test article applications for each subject. The date of the first application of test article will be recorded on the Study Medication Compliance Form. This form will also be used to record any changes from the twice daily 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 the End of Study CRF.

A Subject Diary will be dispensed to subjects to record the application time of all 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

Upon completion or termination of the study all test article containers must be returned to the Sponsor or designee. All missing containers of test article must be explained on the completed Test Article Accountability Log. The study site must keep the original Label Pages and Test Article Accountability Log in the study file. A photocopy of the Test Article Accountability Log and Label Pages will be returned to TI.

All shipments of returned test article must be clearly labeled with the investigator's name, address, and the protocol number.

APPENDIX 4 COSYNTROPIN PACKAGE INSERT

CORTROSYN - cosyntropin injection, powder, lyophilized, for solution
Amphastar Pharmaceuticals, Inc.

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 residue. 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.

CONTRAINDICATIONS

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.
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APPENDIX 5 PROTOCOL AMENDMENTS

PROTOCOL AMENDMENT # 1
Date of Amendment: 04 November 2015

PROTOCOL AMENDMENT # 2
Date of Amendment: August 5, 2016

Summary:
The protocol was amended as follows:

Specfic Changes: Added text has been **bolded** and deleted text has been ~~redlined~~.

Section Number / Name	Specific Change
Title Page	**PROTOCOL NUMBER: 177-0551-201**~~000-0551-209~~ **TI PROJECT NUMBER: 177-0551-201**~~000-0551-209~~ ... **AMENDMENT #2: August 5, 2016** **FILENAME: 177-0551-201_pro_05Aug2016_v3.0.docx** **SPONSOR:** Sun Pharmaceutical Industries, Inc. (a Sun Pharma Company)* 270 Prospect Plains Rd. Cranbury, NJ 08512 ~~Ferndale Laboratories, Inc., 780 West Eight Mile Road, Ferndale, MI 48220~~ **SPONSOR REPRESENTATIVE:** Syed Qadry, Ph.D., Sr. Manager, Regulatory Affairs~~Sarah Van Hoof, Director, Regulatory Affairs & Compliance~~ ... ... This information contained in this document is confidential and proprietary property of **Sun Pharmaceutical**

	Industries, Inc. (a Sun Pharma Company) ~~Ferndale Laboratories, Inc~~.
Protocol Approval	The following individuals approve version **3**~~2~~.0 of the **177-0551-201**~~000-0551-209~~ protocol dated **August 5, 2016**~~November 4, 2015~~. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.
Study Acknowledgement	I have read this protocol and agree that it contains all the details necessary to conduct the study as described. I will conduct this study following this protocol and will make a reasonable effort to complete the study in the time noted. I will provide the contents of this protocol to study staff under my direct supervision that need to know the contents to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the test articles. I will provide the contents of the protocol to the responsible Institutional Review Board(s). These disclosures may be made; providing the contents are not used in any other clinical study and they are not disclosed to any other person or entity without prior written consent from **Sun Pharma**~~FLI~~. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to **Sun Pharma**~~FLI~~ of any such disclosure. I understand the study may be terminated or enrollment suspended at any time by **Sun Pharma**~~FLI~~, 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 **Sun Pharma**~~FLI~~ and must be treated in the same manner as the contents of this protocol. … Protocol Number: **177-0551-201**~~000-0551-209~~ Version: ~~2~~**3**.0 Date of final version: **August 5, 2016**~~November 4, 2015~~
Synopsis, Study Procedures	Post-Treatment Follow-up Visits (Suppressed Subjects Only): Any subjects who have evidence of adrenal suppression at EOS will return approximately every four (4) weeks BUT no sooner than four (4) weeks (28 days) after the EOS visit, and subsequently approximately every four (4) weeks BUT no earlier than every four (4) weeks (>28 days) thereafter for CST until the adrenal response returns to normal. **Subjects with other ongoing AEs that require follow-up may also be followed per the discretion of the investigator.**
1. Background	Halobetasol propionate (HBP) is a well-known corticosteroid with anti-inflammatory properties. It is indicated for the local topical treatment of various inflammatory skin disorders (e.g., psoriasis).
6.1 Description	
10.6 Post-Treatment Follow-Up Visits – Suppressed Subjects Only	These visits are only required for subjects who have demonstrated abnormal CST consistent with suppression at the end of study and are returning for the follow-up CST as per Section 13.1.1. **Subjects with other ongoing AEs that require follow-up may also be followed per the discretion of the investigator.**
Section 13.1 Cosyntropin Stimulation Test (CST)	Perform the cosyntropin stimulation test as follows:

	• Collect a pre-stimulation blood sample **(approximately 6-7 mL)** as specified in the Laboratory Manual. • Reconstitute one vial of cosyntropin (0.25 milligrams) in sodium chloride for injection USP (the volume of sodium chloride in the package insert for Cortrosyn [Appendix 4] is 2 to 5 mL). • Inject the cosyntropin intravenously (the length of time during which the cosyntropin should be injected is 2 minutes [Appendix 4]). • Thirty minutes after completing the cosyntropin injection collect a post-stimulation blood sample **(approximately 6-7 mL)** as specified in the Laboratory Manual.
13.3 Pharmacokinetic Tests	**Blood (approximately 5 mL) for PK analysis will be drawn three times: at Screening (pre-application, time=0) and at Day 8 and Day 15 (unless IGA=0 at Day 8), approximately 12 hours after the dose on the previous day.** All eligible subjects will have blood drawn at Screening for baseline drug concentration in plasma.
15.2 Serious Adverse Event (SAE)	An event that is serious must be recorded on the AE CRF and on the Therapeutics, Inc. SAE Report Form, and requires expeditious handling to comply with regulatory requirements. **SAEs will also be reported by TI to the Sponsor's pharmacovigilance team.**
17.1 Test Article Information	
Appendix 1	SAMPLE SUBJECT INSTRUCTION SHEET FOR PROTOCOL **177-0551-201**~~000-0551-209~~
Appendix 2	SAMPLE SUBJECT DIARY for PROTOCOL **177-0551-201**~~000-0551-209~~
Appendix 3, A3.1 Test Article Packaging and Labeling	**Test Article**~~Bottle~~ Labeling