PROTOCOL SYNOPSIS

Title	An Open Label Evaluation of the Adrenal Suppression Potential and Pharmacokinetic Properties of Twice Daily Halobetasol Propionate Foam, 0.05% in Subjects 12 to Less Than 18 Years of Age with Plaque Psoriasis Receiving Two Weeks of Treatment
Study Type	Phase 4 in the United States (US) sites, Phase 2 in the non-US sites, as necessary.
Test Article	Halobetasol Propionate (HBP) Foam, 0.05%
Study Objective	The objective of this study is to determine the adrenal suppression potential and the pharmacokinetic (PK) properties of HBP Foam, 0.05% applied twice daily in subjects who are 12 to less than 18 years of age with stable plaque psoriasis.
Study Design	An open label, multicenter study.
Treatment Groups	All subjects will receive HBP Foam, 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 12 to less than 18 years of age 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 12 sites in the US and Europe 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 and is 12 to less than 18 years of age (i.e., at least 12 years old, but not yet reached their 18th birthday at the time of enrollment). 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. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at the next study visit to continue study participation.

	3. Subject has a clinical diagnosis of stable plaque psoriasis involving a minimum of 10% body surface area (BSA)[1] (excluding the face, scalp, groin, axillae, and other intertriginous areas). 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][4] 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 days 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.

[1] For this evaluation 1% BSA is approximately equivalent to the area of the subject's closed hand (palm and fingers held together).
[2] UPT must have a minimum sensitivity of 25 mIU ß-HCG/mL.
[3] Effective forms of birth control include a) hormonal contraceptives [e.g., oral, transdermal, injectable, implantable, or vaginal ring] (see next footnote), b) intrauterine device (IUD) for at least one week prior to test article application, c) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], d) monogamous relationship with a partner who is sterile [e.g., vasectomy performed at least six months prior to study entry], or e) total abstinence for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.
[4] Females taking hormonal therapy must be on treatment prior to study entry, continued per label, and must not change their dosing regimen during the study; treatment must be for (1) oral: at least one complete cycle (e.g., four to eight weeks); (2) transdermal, injectable (e.g., Depo-Provera), implantable or vaginal ring (e.g., NuvaRing): at least one week.

	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 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.
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 demographics and medical history, including concomitant medications, recorded and Inclusion/Exclusion (I/E) criteria, including percent BSA affected with disease, 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. Blood and urine samples will be taken for clinical laboratory tests (chemistry, hematology, and urinalysis). Subjects will have a Screening CST that will 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. Any adverse events (AEs) will be recorded. 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. The subject will be scheduled for the Day 1/Baseline 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. Review clinical laboratory tests (chemistry, hematology, and urinalysis); repeat any lab findings that are abnormal and deemed clinically significant by the investigator per protocol to confirm the findings. Study staff will reconfirm medical history and will record any changes in concomitant medications. 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 and photographs (optional) will be taken. IGA score will be recorded. Study staff will document percent BSA affected with disease in the Treatment Area and the percent BSA to be treated with the test article during the study. Baseline local skin reactions (LSRs) will be recorded prior to test article application. The weight of the canisters will be measured prior to dispensing and test article accountability will be documented. 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 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. The subject will be scheduled for the Day 8 visit. 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). Visit 3 (Day 8 ± 1): If the subject's psoriatic lesions within the Treatment Area are not completely clear, then the subject will complete these Visit 3 (Day 8 ± 1) procedures. However, if the subject's psoriatic lesions within the Treatment Area are completely clear per the Investigator's assessment (i.e., IGA=0), then the subject will complete the Visit 4/EOS procedures; if the CST cannot be performed on Day 8, then the subject will complete Visit 3 procedures, continue dosing of test article, and return on Day 9 (see Optional Visit) to complete the EOS procedures. Subjects who are clear at Day 8, complete CST on Day 8 (or Day 9), and have all EOS procedures completed on Day 8 (or Day 9) will exit the study at Day 8 (or Day 9) following a normal CST result. Subjects will return to the clinic on Day 8 for the study staff to record IGA score, percent BSA affected with disease in the Treatment Area, percent BSA to be treated, review test article compliance (i.e., Subject Diary will be collected, reviewed, and dispensed, as necessary), and collect information on concomitant medications, AEs, and LSRs. Test article accountability will be documented.

	Subjects will have blood drawn on the morning of Day 8 to assess drug concentrations in plasma (trough values - ~12 hours after previous dose). Subjects 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 the next clinic visit. Any AEs or LSRs (i.e., burning/stinging only) post-application will be recorded. The subject will be scheduled for the next visit. Day 9 (Optional Visit - for Subjects that are clear at Visit 3, Day 8): On the following day (Day 9), subjects cleared by Day 8 who could not have a CST performed on Day 8 will have a UPT (females only) and have a CST performed within ± 1 hour of Screening CST and should, to the extent possible, be initiated between 7 and 9AM. Photographs (optional) will be taken. Any AEs and LSRs will be recorded, any concomitant medications will be documented, all test article and subject diaries will be collected, and the subject will exit the study following a normal CST result. Visit 4 (Day 15 ± 2 or EOS): Subjects will return to the clinic for the study staff to collect information on AEs, LSRs, concomitant medications, take blood and urine samples for clinical laboratory tests (chemistry, hematology, and urinalysis), draw a final trough PK blood sample prior (~12 hours following previous dose) to EOS CST, and perform the EOS CST. The EOS visit should be scheduled for the morning so that the EOS CST will occur at the same time (± one hour) as the CST performed at Visit 1 (Screening) and should, to the extent possible, be initiated between 7 and 9AM. If any of these subjects have adrenal suppression (defined as post-CST cortisol level ≤ 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 in the Treatment Area and photographs (optional) will be taken. All female subjects will have a UPT. All test article and subject diaries will be collected. The subject will exit the study following a normal CST result. Post-Treatment Follow-up Visits (Suppressed Subjects Only): Any subject who has 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. Follow-up CST will be performed within ± 1 hour of Screening CST and should, to the extent possible, be initiated between 7 to 9AM. It is important subjects remain off of all forms of steroid therapy (systemic, topical, injectable, etc.) during this post-treatment assessment period. See Section 9.3 for procedures to be performed at these post-treatment follow-up visits.
Study Measurements	The following assessments will be performed per the schedule of events. 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 (plaque elevation, scaling, and erythema) with the IGA score at each visit representing the average of plaque elevation, scaling, or erythema that is present amongst all of the lesions eligible for treatment. Percent Body Surface Area Affected with Disease: The percent BSA affected with psoriasis in the Treatment Area (excluding the face, scalp, groin, axillae, and other intertriginous areas) will be estimated at the Screening Visit, Baseline Visit/Day 1, Day 8, and Day 15. Percent Body Surface Area Treated with Test Article: The percent BSA treated with the test article will be estimated at Baseline Visit/Day 1 and Day 8 (for subjects who have not cleared). 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 canisters of test article will be weighed at each visit. 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. Burning/stinging will be evaluated post-application at Baseline Visit/Day 1 and Day 8 (for subject who have not cleared). Adverse Events: All AEs will be recorded. At each visit after the Baseline Visit/Day 1, subjects will also be questioned specifically about the status of any ongoing AEs. Clinical Laboratory Tests Urine and blood samples will be collected from each subject for safety laboratory analysis at Visit 1/Screening, Visit 2/Baseline (if applicable), and Visit 4/EOS. Any new or worsening clinically significant abnormalities at Visit 4/EOS will be recorded as AEs. Cosyntropin Stimulation Test: The EOS visit (i.e., the end of the assigned treatment period) should be scheduled in the morning so that the CST will occur at the same time (± one hour) as the CST performed at Visit 1 (Screening). The Screening CST will be initiated between 7 and 9AM; all follow-up CSTs should, to the extent possible, be initiated between 7 and 9AM.

	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 (± 30 minutes) 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 ≤ 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 approximately 12 hours (± 30 minutes) post-treatment. Other Safety Endpoints - AEs, LSRs, clinical laboratory tests, 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/PK 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. Subjects discontinued from the study at Visit 2 due to ineligibility criteria (screen failures) will be excluded from the HPA axis suppression summaries. Subjects included in the PK analysis (PK population) must not have any significant protocol deviations and must have 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. ***Safety Analyses:*** Dosing Compliance Descriptive statistics will be used to summarize test article compliance. 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 and average amount of test article used per application by each subject. An approximation of the amount of test article applied per cm^2 will be determined based on the average amount of test article used per application and an estimate of the percent BSA treated with the test article at Visit 2/Baseline. The BSA treated with test article (in square centimeters) will be determined from the Mosteller calculation [1]. Urine Pregnancy Tests A listing of UPT results will 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 electronic case report forms (eCRFs) 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. Clinical Laboratory Tests Clinical laboratory tests will be evaluated for any clinically significant changes during the study period. All laboratory data (hematology, chemistry, and urinalysis) will be listed and reported in the units received by the laboratory. Shift tables by analyte and by out of range flag will be presented to facilitate the evaluation of change from Visit 1/Screening to Visit 4/EOS. HPA Axis Suppression Analysis HPA axis responses to CST will be dichotomized to normal and abnormal. An abnormal HPA axis response (HPA suppression) is defined as a 30-minute post-stimulation serum cortisol level of $\leq$18 µg/dL at the end of study. The proportion of subjects manifesting laboratory evidence of adrenal suppression at the end of study 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.

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