STATISTICAL ANALYSIS PLAN

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PROTOCOL 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
ORIGINAL PROTOCOL DATE:	October 21, 2015
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ABBREVIATIONS

AE	Adverse Event
BSA	Body Surface Area
CSR	Clinical Study Report
CST	Cosyntropin Stimulation Test
eCRF	electronic Case Report Form
EOS	End of Study
HBP	Halobetasol Propionate
HPA	Hypothalamic-Pituitary-Adrenal
IGA	Investigator's Global Assessment
LSR	Local Skin Reaction
mITT	modified Intent-to-Treat
PK	Pharmacokinetic
PT	Preferred Term
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TI	Therapeutics, Inc.
UPT	Urine Pregnancy Test

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol 177-0551-201, "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".

This SAP was created using Clinical Protocol 177-0551-201 Version 3.0 dated August 5, 2016, Administrative Amendment #1 dated October 28, 2016, and the Case Report Forms (CRF) Version 1.0 dated December 21, 2016.

2. PURPOSE OF THE ANALYSES

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for Protocol 171-0551-201. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objective of this study is to determine the adrenal suppression potential and the pharmacokinetic (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.

3.2 Efficacy Endpoints

The primary objective of this study is to assess safety, however, Investigator's Global Assessment (IGA) and percent body surface area (BSA) treated and affected with disease will be assessed to document any changes that are observed with regard to IGA and percent BSA.

3.3 Safety Endpoints

3.3.1 HPA Axis Response to Cosyntropin

Hypothalamic-pituitary-adrenal (HPA) axis responses to stimulation by cosyntropin will be dichotomized to "normal" and "abnormal".

3.3.2 Plasma Levels of Halobetasol Propionate

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

3.3.3 Other Safety Endpoints

Other safety endpoints will include adverse events (AEs), local skin reactions (LSRs) associated with topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, and folliculitis, urine pregnancy tests (UPTs), dosing compliance, and extent of exposure.

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 cosyntropin stimulation test (CST) to assess their HPA axis response at Visit 1 (Screening 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. 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).

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 PK blood sample collected approximately 12 hours after their Day 14 evening application and just prior to the initiation of the CST.

4.1 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[2]*	*Visit 4 EOS Day 15[3,4] (± 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)[5]	X	X	X[6]	X[6]	X
Cosyntropin Stimulation Test (CST)	X[7]	Confirm eligibility[7]	X[8]	X[8]	X[8]
Percent BSA Affected with Disease	Confirm eligibility	X	X		X
Investigator's Global Assessment (IGA) Score	X	X	X	X[6]	X[6]
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[6] (withhold AM application until after trough PK blood draw)		
Concomitant Medication Assessments	X	X	X	X[6]	X
Adverse Events Assessment	X	X	X	X[6]	X
Record Local Skin Reactions		X (pre- and post-test article application)[10]	X (pre- and post-test article application)[9]	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[2]*	*Visit 4 EOS Day 15[3,4] (± 2) or Early Term*
Drug Accountability (with Weights)		X	X	X[6]	X[10]
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 This visit is to take place on the day following Visit 3/Day 8.
3 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.
4 Final scheduled visit occurs at Day 15 $\pm$ 2.
5 All female subjects will have a UPT at Screening, Baseline and at the end of study.

7 Subjects with an abnormal CST at Screening will be discontinued from the study.
8 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.
9 All LSRs will be assessed pre-application and only burning/stinging will be assessed post-application.
10 Weigh and collect test articles at the end of study visit.

5. DEFINITIONS

- The "Treatment Area" is defined as the entire body exclusive of the face, scalp, groin, axillae, or other intertriginous areas.
- End of Study (EOS) visit is the visit at which psoriasis has cleared or end of the assigned treatment period.
- A completed subject is a subject who completes the treatment as specified in the protocol and who completes the EOS evaluations.
- A subject's psoriasis is defined as cleared if, at any visit, the investigator reports a score of zero (0) for IGA.
- Visit 1 is designated as Screening.
- Visit 2 is designated as Baseline.
- Visit 3 is designated as Day 8.
- Visit 4 is designated as Day 15.

6. CLINICAL EVALUATIONS

6.1 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). 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:

6.2 Percent Body Surface Area 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.

6.3 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. In most cases there is no difference between percent BSA affected and percent BSA treated unless the affected BSA is too large to be treated with the drug dosing limitation of 50 grams per week (e.g., 3.5 grams per application). The percent BSA to be treated will be estimated at Baseline and Day 8.

7. SAFETY EVALUATIONS

7.1 Cosyntropin Stimulation Test

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

At the EOS visit, 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. If these conditions are not met, the subject should be rescheduled for CST on the next day.

If the results of the Visit 1 (Screening) CST indicate the subject has an abnormal HPA axis response (defined as a post-stimulation serum cortisol level of ≤ 18µg/dL), the subject should be classified as a screen failure and withdrawn from the study.

If a subject's EOS CST results show an abnormal HPA axis response (defined as a post-stimulation serum cortisol level of ≤ 18µg/dL), the test article will be considered to have caused adrenal suppression in the subject. The subject will be required to return for additional follow-up visits, no less than every four weeks, until the HPA axis response has been documented to return to normal.

7.2 Pharmacokinetic Tests

Blood for PK analysis will be drawn three times: at Screening (pre-application, time=0), 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. 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.

7.3 Adverse Events

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

The severity of an AE will be recorded as mild, moderate, or severe. The relationship between an AE and the test article will be classified as definitely related, probably related, possibly related, unlikely related, or not related.

7.4 Local Skin Reactions

At all post-screening visits, the investigator or designee will observe or directly query the subject regarding LSRs known to be associated with topical application of corticosteroids. The severity of the following LSRs: telangiectasia, skin atrophy, burning/stinging and folliculitis will be recorded as 0-none, 1-mild, 2-moderate, or 3-severe. A LSR is to be recorded as an AE only if therapy or discontinuation of test article is required.

7.5 Urine Pregnancy Tests

A UPT will be performed on all female subjects at Visit 1 (prior to CST), Visit 2 (prior to treatment), and at EOS or if the subject withdraws prematurely.

8. STATISTICAL METHODS

8.1 General Considerations

This section presents the statistical approaches that are anticipated for the analysis of the study data. These approaches may at times require modifications due to unanticipated features of the data. Deviations from analyses summarized in this document will be noted in the CSR.

All statistical analyses and summaries will be prepared using SAS® version 9.4 unless otherwise stated.

Frequency counts and percentages will be reported for categorical data and sample size, mean, standard deviation (SD), median, minimum and maximum values will be reported for the continuous variables.

In general, all summary tables will be supported by a relevant subject data listing which will be sorted by study site, subject identification, and visit, as applicable. Figures may be created to aid in the interpretation of results.

8.2 Analysis Populations

8.2.1 Safety Population

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.

8.2.2 Evaluable Population

The Evaluable population will include those subjects in the Safety population who have both Screening and EOS serum cortisol data (pre- and post-cosyntropin stimulation) and meet the following criteria:

- Meets all inclusion/exclusion criteria, including normal response to cosyntropin stimulation defined as a Screening CST with a 30-minute post-stimulation cortisol level >18 µg/dL.
- Screening and EOS CST were conducted between 7-9 AM.
- EOS CST was conducted within ± 1 hour of the Screening CST.
- Applied at least 80% and no more than 120% of the expected number of applications and applied the final dose no more than 14 hours prior to the start of the CST test.

- Has not taken or applied any medications that may interfere with HPA axis function.
- Do not have any other significant protocol deviations.

HPA axis suppression analysis will be conducted on the Evaluable and Safety populations.

8.2.3 Pharmacokinetic Population

Subjects included in the PK analysis (PK population) will include those subjects in the Safety population who do not have any significant protocol deviations and must have at least an 80% - 120% dose compliance based on number of applications.

8.3 Final Analyses and Reporting

Final database lock will occur after all subjects have completed the study assessment period (or withdrew from the study prematurely) and all subject data have been monitored and all queries resolved.

Further exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not described in this SAP will be clearly identified as such in the CSR.

8.4 Sample Size

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.

8.5 Subject Disposition

The number and percent of subjects who were randomized in the study, in each analysis population, who completed the study, who withdrew from the study, and their reasons for withdrawal will be summarized. Subject disposition will be summarized using all subjects who signed informed consent/assent forms and were enrolled in the study.

Subject data listings of the protocol deviations, if any, and analysis population identification will be provided.

8.6 Screening and Baseline Assessments

8.6.1 Demographics

Demographic information including sex, age, race, and ethnicity will be summarized for the Safety, Evaluable, and PK populations, as well as, screen failures.

8.6.2 Medical History

Medical history will be provided in a subject data listing for the Safety population.

8.6.3 Physical Examination

Physical examination abnormalities will not be provided separately, but will be included with medical history.

8.6.4 Vital Signs, Height, and Weight

Descriptive statistics will be provided for height, weight, temperature, systolic and diastolic blood pressure, heart rate, and respiration rate for the Safety population.

8.6.5 Baseline Clinical Evaluations

The Screening and Baseline severity scores for IGA will be tabulated for the Safety, Evaluable, and PK populations. The frequency distribution of the body areas affected by plaque psoriasis will be presented. Descriptive statistics will be provided for the Percent BSA Affected and the Percent BSA to be Treated.

8.6.6 Baseline Local Skin Reactions

The frequency distributions of the Baseline severities of LSRs associated with topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, and folliculitis will be summarized for the Safety populations.

8.7 Dosing Compliance

Descriptive statistics will be used to summarize test article compliance for the Evaluable and PK populations. Measures of test article compliance will include the duration of treatment (number of days dosed = last dose date - first dose date + 1), the total number of applications (determined from the actual number of applications reported by the subject), and the percent of expected doses applied. The expected number of doses for subjects who are clear at Day 8 and discontinue from the study is 14. Subjects who continue to Day 15 or early term will have the compliance rate based on an expected 28 doses. 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.

8.8 Efficacy Evaluation

8.8.1 Analysis of Efficacy

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. Frequency distributions of the observed and change from Baseline IGA severity scores will be presented for each visit for the Evaluable population.

Descriptive statistics will be provided for observed and changes from Baseline with respect to both the percent BSA affected and to be treated for the Evaluable and PK populations.

8.8.2 Statistical / Analytical Issues

8.8.2.1 Handling of Dropouts or Missing Data

All summaries will be based on observed data only. Imputation of missing clinical data values will not be performed. For the PK analyses, concentrations reported as below the lower limit of quantitation will be imputed as zero.

8.8.2.2 Interim Analyses

No interim analyses will be performed.

8.8.2.3 Multicenter Studies

Data tabulations will be per study site, as well as, overall.

8.8.2.4 Multiple Comparisons / Multiplicity

Not applicable.

8.8.2.5 Examination of Subgroups

No subgroup analyses will be performed.

8.9 Safety Evaluation

8.9.1 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 Safety, Evaluable, and PK populations.

8.9.2 Adverse Events

All AEs reported during the study will be listed, documenting onset, whether therapy was required, any change in test article dosing, severity, possible relationship to test article, and outcome. Verbatim terms on the CRFs will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. For all AE summaries, if a subject has more than one AE within a PT, the subject is counted once in that PT. If a subject has more than one AE within a SOC, the subject is similarly counted once in that SOC.

The number and percentage of unique subjects reporting any local and systemic treatment-emergent AE will be summarized by SOC and PT. The number and percent of unique subjects reporting any local and systemic TEAE will also be summarized by SOC, PT, and maximum severity (mild, moderate, severe) and closest relationship to test article (not related, unlikely, possibly, probably, definitely related). AE summaries will utilize the Safety population.

8.9.3 HPA Axis Suppression Analyses

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.

The proportion of subjects manifesting laboratory based evidence of adrenal suppression at EOS (as defined in Section 3.3.1) will be presented along with 95% confidence intervals for the Evaluable and Safety populations. The observed serum cortisol levels (pre-and post-cosyntropin stimulation) and the changes in serum cortisol levels after stimulation at Screening, EOS, and, if any, at follow-up visits will also be summarized. In addition, descriptive statistics for the daily dose of test article will be tabulated separately for suppressed and non-suppressed subjects.

8.9.4 Pharmacokinetic Analyses

Morning trough concentrations of HBP in plasma at Screening, Day 8 and Day 15 will be summarized for the PK population using geometric mean, coefficient of variation in addition to n, mean, median, standard deviation, minimum and maximum.

8.9.5 Local Skin Reactions

The frequency distributions of the observed and change from Baseline severities of LSRs associated with topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, and folliculitis will be summarized for the Safety population at Baseline and all follow-up visits.

8.9.6 Urine Pregnancy Tests

A listing of UPT results will also be provided for the Safety population.

8.9.7 Concomitant Medications and Concurrent Therapies/Procedures

A subject listing of the concomitant medications will be provided. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version September 2017 and summarized by ATC Level 3 for the Safety population. A separate listing of concurrent procedures and therapies will also be provided. No coding of therapies or procedures will be performed.

9. CHANGES TO PROTOCOL

The protocol defined the Safety, modified Intent-to-Treat (mITT), and PK populations. Since an efficacy analysis is not the primary endpoint for this protocol, the mITT population has been replaced with the Evaluable population to be used for the analysis of HPA suppression response. Requirements for inclusion in the Evaluable population are specified so that the CST are consistent between the subjects.

The protocol included the determination of the approximate amount of test article applied per cm^2 prior to the collection of the PK samples at Visit 3 from the estimate of the percent BSA treated with the test article and the amount of test article applied based on the before and after weights of the dose prior to the blood draws. This data was not captured for this study, therefore, this determination will not be performed.