

**A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP
COMPARISON OF HALOBETASOL PROPIONATE FOAM, 0.05% VERSUS VEHICLE
FOAM IN SUBJECTS WITH PLAQUE PSORIASIS**

PROTOCOL NUMBER: 122-0551-310

TI PROJECT NUMBER: 122-0551-310

IND NUMBER: [REDACTED]

ORIGINAL PROTOCOL: March 16, 2016

AMENDMENT #1: June 17, 2016

FILENAME: [REDACTED]

SPONSOR: [REDACTED]

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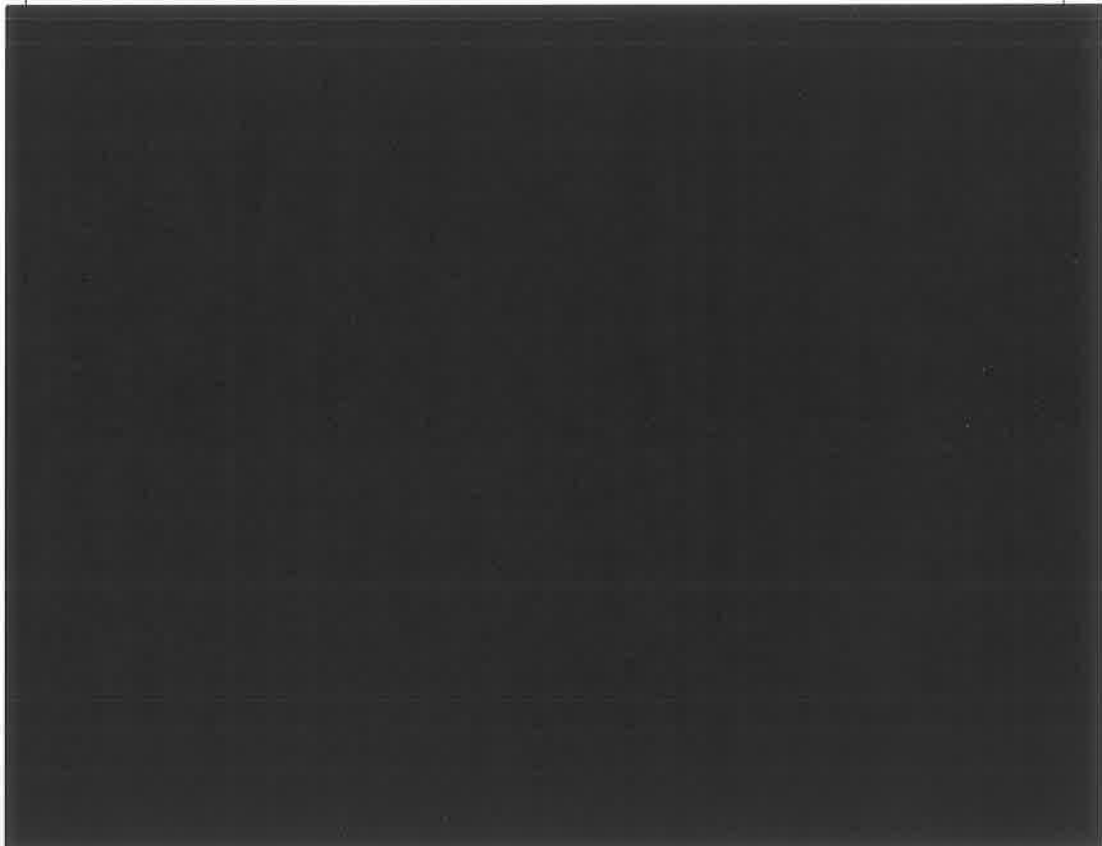
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Product Name: Halobetasol Propionate Foam, 0.05%
Sponsor Name: [REDACTED]

IND: 107,302
Protocol: 122-0551-310; v2.0

PROTOCOL APPROVAL

The following individuals approve version 2.0 of the 122-0551-310 protocol dated June 17, 2016. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.



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STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to [REDACTED]

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 [REDACTED]. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to [REDACTED] of any such disclosure.

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

Printed Name of Principal Investigator

Investigator Signature

Date

Protocol number: 122-0551-310

Site number: _____

Version: 2.0

Date of final version: June 17, 2016

Product Name: Halobetasol Propionate Foam, 0.05%
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PROTOCOL SYNOPSIS

Title	A Multicenter, Randomized, Double-Blind, Parallel Group Comparison of Halobetasol Propionate Foam, 0.05% versus Vehicle Foam in Subjects with Plaque Psoriasis
Study Type	Phase 3
Test Articles	1. Halobetasol Propionate Foam, 0.05% (HBP Foam) 2. Halobetasol Propionate Foam Vehicle (VEH Foam)
Study Objective	The primary objective is to determine and compare the efficacy and safety of HBP Foam and the VEH Foam applied twice daily for two weeks (Study Day 15 + 3 days) in subjects with plaque psoriasis.
Study Design	Multicenter, randomized, double-blind, vehicle-controlled, parallel group comparison study.
Treatment Groups	Eligible subjects will be randomized (1:1) to one of two treatment groups: HBP Foam or VEH Foam. The assigned test article will be applied by the subjects twice daily (maximum of approximately 50 grams per week).
Duration of Treatment	Two weeks (Study Day 15 + 3 days)
Duration of Study	Study duration is approximately two (2) weeks for an individual subject.
Study Population	Male and female subjects, aged 18 years or older with stable plaque psoriasis.
Total Number of Subjects	Approximately 400 subjects will be enrolled with the following approximate numbers of subjects assigned to each test article: a) 200 HBP Foam and b) 200 VEH Foam.
Number of Sites	Approximately 20 sites will participate in the study.
Inclusion Criteria	<p>To enter the study, a subject must meet the following criteria:</p> <ol style="list-style-type: none">1. Subject is male or non-pregnant female and is at least 18 years of age at the time of the Screening Visit.2. Subject has provided written informed consent.3. Subject is willing and able to apply the test article(s) as directed, comply with study instructions and commit to all follow-up visits for the duration of the study.4. Subject has a clinical diagnosis of stable plaque psoriasis involving [REDACTED] body surface area (BSA)¹ (excluding the face, scalp, groin, axillae and other intertriginous areas).

¹ 1% BSA is approximately equal to the surface area of the subject's palm and fingers, with the fingers extended yet grouped together, creating a flat oval-like surface area. For BSA determination residual discoloration (pigmentation and/or erythema) should not be included.

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	<ol style="list-style-type: none">5. Subject has an Investigator's Global Assessment (IGA) score of at least three (3 = moderate) at the Baseline Visit.6. Females must be post-menopausal², surgically sterile³ or use an effective method of birth control^{4,5} with a negative urine pregnancy test (UPT)⁶ at the Baseline Visit.
Exclusion Criteria	<p>A subject is ineligible to enter the study if he/she meets one or more of the following criteria:</p> <ol style="list-style-type: none">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, or which exposes the subject to an unacceptable risk by study participation.4. Subject has used any phototherapy (including laser), photo-chemotherapy, or other forms of photo based therapy for the treatment of their psoriasis within 30 days prior to the Baseline Visit.5. Subject has used any systemic methotrexate, retinoids, systemic corticosteroids [including intralesional, intra-articular, and intramuscular corticosteroids], cyclosporine or analogous products within 90 days prior to the Baseline Visit.6. Subject has used any systemic biologic therapy (i.e., FDA-approved or experimental therapy) within five (5) half-lives of the biologic prior to the Baseline Visit. Published or documented half-life of the product provided by the commercial supplier or Sponsor should be used to establish this value.7. Subject had prolonged exposure to natural or artificial sources of ultraviolet radiation within 30 days prior to the Baseline Visit or is intending to have such exposure during the study which in the opinion of the investigator is thought to modify the subject's disease.8. Subject has used topical body (excluding the scalp) psoriasis therapy (including coal tar, anthralin, steroids, retinoids, and vitamin D analogs) within 14 days prior to the Baseline Visit.9. Subject has used emollients/moisturizers on areas to be treated within four hours prior to clinical evaluation at the Baseline Visit.

² Defined as amenorrhea greater than 12 consecutive months in women 55 years of age and older.

³ Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment) or bilateral oophorectomy.

⁴ Effective forms of birth control include hormonal contraceptives [oral, injectable, transdermal, or intravaginal], or intrauterine device (IUD) for two cycles (e.g., 8 weeks) (note: for Depo-Provera the requirement is at least 7 days after injection) 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.

⁵ Women of childbearing potential (WOCBP) taking hormonal therapy must be on treatment for two cycles (e.g., 8 weeks) prior to study entry.

⁶ UPTs must have a minimum sensitivity of 25 mIU β -hCG/mL.

	<ol style="list-style-type: none"> 10. Subject is currently using lithium or Plaquenil (hydroxychloroquine). 11. Subject is currently using a beta-blocking medication (e.g., propranolol) or angiotensin converting enzyme (ACE) inhibitor at a dose that has not been stabilized, in the opinion of the investigator. 12. Subject has a history of sensitivity to corticosteroids or any of the ingredients in the test articles (see Section 6.1). 13. Subject is pregnant, lactating, or is planning to become pregnant during the study. 14. Subject is currently enrolled in an investigational drug or device study. 15. Subject has used an investigational drug or investigational device treatment within 30 days prior to the Baseline Visit. 16. Subject has been previously enrolled in this study and treated with a test article. 17. 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	<ol style="list-style-type: none"> 1. <u>Visit 1 (Screening/Baseline Visit, Day 1)</u>: At Visit 1, study staff will explain the study procedures and an informed consent must be signed prior to the initiation of any study-related procedures. At this visit, consenting subjects will have their medical history/demographics, inclusion/exclusion (I/E) criteria, and concomitant medications/therapies reviewed to determine subject eligibility. Subjects that require a "washout" period prior to enrollment into the treatment phase to meet I/E criteria requirements will be required to return to the clinic within 45 days to complete the remaining activities. Subjects who require "washout" for longer than 45 days will be re-consented. All WOCBP must have a negative UPT. A limited physical exam, clinical evaluations, and photography (select sites only) will be performed prior to test article application. The Treatment Area is defined as all areas of the body (excluding the face, scalp, groin, axillae and other intertriginous areas). The percent BSA with active psoriasis in the Treatment Area and Baseline local skin reactions (LSRs) will be recorded prior to test article application. Subjects who meet all inclusion criteria and no exclusion criteria will be randomized and assigned to the next available (lowest) subject number in ascending order. The test article will be weighed prior to dispensing to subjects. Subjects will apply the assigned test article to all psoriatic plaques in the Treatment Area twice daily for the assigned treatment period. Subjects will apply the first dose of the assigned test article to all plaques in the Treatment Area under staff supervision. At this visit, each subject will be given a subject instruction sheet and the study personnel will review the subject instruction sheet including how and where to dispense and apply test article to all the psoriatic plaques. Any adverse events (AEs) post-application will be recorded. A subject diary will also be given to each subject with completion instructions. A bland emollient will be dispensed to the subject, as required, to be used only on non-diseased skin or diseased skin not being treated with the test article (i.e., the face, scalp, groin, axillae, and other intertriginous areas). The subject will then be scheduled for Visit 2.

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	<p>2. <u>Visit 2 (Follow-Up, Day 8 ± 2)</u>: Subjects enrolled into the study will return to the clinic on Day 8 for the study staff to perform the clinical evaluations (excluding pruritus), photography (at the discretion of the investigator at designated study sites only), record percent BSA with active psoriasis in the Treatment Area, collect and review the Subject Diary for test article compliance and review completion requirements (as needed), update concomitant medications, record AEs and LSRs, collect and weigh used test article canisters, and weigh/dispense an additional canister, if necessary. Subjects will continue treatment and will be scheduled for Visit 3.</p> <p>3. <u>Visit 3 (Final Visit, Day 15 ± 3)</u>: Subjects will return to the clinic on Day 15 for the study staff to perform the clinical evaluations, photography (designated study sites only), record percent BSA with active psoriasis in the Treatment Area, collect and review the Subject Diary for test article compliance, update concomitant medications, record AEs and LSRs, collect and weigh all used and unused canisters of test article as all canisters of test article that have been dispensed must be accounted for. A UPT will be performed, if applicable.</p>
Study Measurements	<p>At each visit, the following assessments will be performed:</p> <p><u>Efficacy:</u> <u>Investigator's Global Assessment (IGA)</u> 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 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. IGA will be assessed on a 5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe.</p> <p><u>Clinical Signs of Psoriasis</u> Scaling, erythema, and plaque elevation will each be scored on a 5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. These evaluations are an assessment of the overall or "average" degree of each of three key characteristics present within all of the subject's psoriatic lesions in the Treatment Area by the investigator or designee.</p> <p><u>Pruritus</u> At the Baseline Visit, prior to the first application of the test article, the subject's overall experience of pruritus within the previous two (2) weeks will be assessed using a questionnaire that assesses the degree, duration, direction, disability, and distribution of the subject's pruritus. At Day 15, the overall experience of pruritus, in the previous two weeks, will be scored using the same questionnaire.</p> <p><u>Body Surface Area with Psoriasis in the Treatment Area</u> The percent (%) BSA with active psoriasis in the Treatment Area will be determined at the Baseline Visit, Week 1 (Day 8), and Week 2 (Day 15) and</p>

	<p>documented. At Baseline, the percent BSA with active psoriasis in the Treatment Area must be 2% to 12%, inclusive.</p> <p>Safety:</p> <p><u>Test Article Compliance</u></p> <p>Subjects will apply the first dose of test article to all psoriatic plaques in 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 dates and times of test article application in their diaries. All canisters of test article will be weighed at each visit and the amount of test article used will be recorded.</p> <p><u>Local Skin Reactions</u></p> <p>At each visit, subjects will also be evaluated for any LSRs within the areas treated with test article associated with the topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, folliculitis, and edema.</p> <p><u>Adverse Events</u></p> <p>All AEs will be recorded. At each visit, subjects will also be questioned specifically about the status of any ongoing AEs.</p>
Study Endpoints	<p>Efficacy Endpoint(s):</p> <p>IGA scores and the clinical signs of psoriasis will be dichotomized to “treatment success” or “treatment failure” where “treatment success” is defined as a score of 0 or 1 representing “cleared” or “almost cleared” with at least a two grade decrease in severity score relative to Baseline.</p> <p>The primary efficacy endpoint will be the proportion of subjects with IGA “treatment success” at Day 15.</p> <p>The key secondary efficacy endpoints are:</p> <ul style="list-style-type: none"> • The proportion of subjects rated a “treatment success” for plaque elevation at Day 15. • The proportion of subjects rated a “treatment success” for scaling at Day 15. • The proportion of subjects rated a “treatment success” for erythema at Day 15. <p>Other efficacy endpoints include:</p> <ul style="list-style-type: none"> • The proportion of subjects with IGA “treatment success” at Day 8. • The proportion of subjects rated a “treatment success” for each of the clinical signs of psoriasis (scaling, erythema, and plaque elevation) at Day 8. • Change from Baseline in pruritus score at Day 15. • Changes in percent BSA with active psoriasis in the Treatment Area at Days 8 and 15. <p>Safety Endpoint(s):</p>

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	<p>Safety endpoints will include assessment of LSRs associated with topical application of corticosteroids (telangiectasia, skin atrophy, burning/stinging, folliculitis, and edema), AEs, and serious adverse events (SAEs).</p>
Sample Size Calculations	<p>A sample size of 200 subjects for each treatment group (i.e., HBP Foam and VEH Foam) is estimated to be sufficient to detect a true treatment difference of “success” rates (20% for HBP Foam versus 9% for VEH Foam) based on Fisher’s Exact Test with a power of 0.85 and a Type I error rate of 0.05 (two-tailed).</p> <p>Approximately 400 subjects are expected to be consented and enrolled into this study and assigned in a 1:1 randomization to one of two treatments: HBP Foam (200) and VEH Foam (200).</p>
Statistical Methods	<p>All statistical processing will be performed using SAS® unless otherwise stated. Statistical significance for the primary efficacy endpoint will be based on a two-tailed test of the null hypothesis at the $\alpha=0.05$ level of significance.</p> <p>Efficacy analyses will be performed primarily for the intent-to-treat (ITT) population. Efficacy analyses using the per-protocol (PP) population will be in support of the ITT analyses.</p> <p>The Safety population will include all subjects enrolled in the study who were dispensed and applied test article at least once. Subjects will apply their first application of the test article in the clinic during their Baseline Visit on Day 1. Subjects enrolled in the study who were randomized and dispensed test article will be considered the ITT population. Subjects will be included in the PP efficacy analyses if they have completed the study without significant protocol deviations. Subjects who discontinue from the study prematurely due to treatment failure, as determined by the investigator, will also be included in the PP population as treatment failures.</p> <p>Demographic and baseline characteristics will be summarized by treatment group for the ITT, PP, and Safety populations. Frequency counts and percentages will be reported for categorical data and the number of subjects with non-missing data (n), mean, median, standard deviation (SD), minimum and maximum will be reported for the continuous variables.</p> <p>Efficacy Analyses:</p> <p>Efficacy will be demonstrated if the proportion of HBP Foam treated-subjects with IGA “treatment success” at Day 15 is statistically significantly greater than the proportion of VEH Foam-treated subjects that are “treatment successes” at Day 15 based on a two-sided test at the $\alpha=0.05$ level of significance. The treatment groups will be compared with respect to IGA treatment success at Day 15 using the Cochran-Mantel-Haenszel (CMH) test stratified by center.</p> <p>Subjects without data at Day 15 will be considered to be treatment failures (i.e., to not have achieved the primary endpoint). Note: this definition includes subjects who drop out of the study prior to Day 15 for any reason.</p>

	<p>Analysis of Key Secondary Endpoints: If the primary analysis is statistically significant ($p < 0.05$), then a “gatekeeping” approach will be used to test the three key secondary endpoints:</p> <ul style="list-style-type: none"> • The proportion of subjects rated a “treatment success” for plaque elevation at Day 15. • The proportion of subjects rated a “treatment success” for scaling at Day 15. • The proportion of subjects rated a “treatment success” for erythema at Day 15. <p>Thus, if the analysis of the first key secondary endpoint is statistically significant at the $\alpha = 0.05$ level of significance, then the second key secondary endpoint will be tested at the $\alpha = 0.05$ level of significance. If this analysis is statistically significant, then the third key secondary endpoint will be tested at the $\alpha = 0.05$ level of significance. However, if any previous analysis (including the primary analysis) is not statistically significant, all subsequent comparisons will be exploratory rather than confirmatory.</p> <p><u>Investigator’s Global Assessment</u> The frequency distributions of IGA scores will be summarized by treatment group at Baseline, and at Days 8 and 15. The proportions of subjects considered a “treatment success” at Days 8 and 15 will be tabulated by treatment group. The treatment groups will be compared with respect to IGA treatment success rates at Day 8 using the CMH test stratified by center.</p> <p><u>Clinical Signs of Psoriasis</u> The frequency distributions of the secondary efficacy endpoints, clinical signs of psoriasis (scaling, erythema, and plaque elevation), will be summarized by treatment group at Baseline, and at Days 8 and 15. The treatment groups will also be compared with respect to “treatment success” rates at Day 8 for each sign of psoriasis using the CMH test stratified by center. Subjects with Baseline scores of 0 or 1 will be excluded unless the corresponding sign score at Day 8 is > 1.</p> <p><u>Pruritus</u> Descriptive statistics of the 5-D Pruritus Scale scores will be provided by treatment group at Baseline and at Day 15. The treatment groups will be compared with respect to the change from Baseline in pruritus score using analysis of covariance with the model including terms for treatment and center with the Baseline pruritus score serving as the covariate.</p> <p><u>BSA with Active Psoriasis in the Treatment Area</u> The changes from Baseline in the percent BSA with active psoriasis in the Treatment Area will be summarized for each treatment group with descriptive statistics at Days 8 and 15.</p> <p><u>Safety Analyses:</u> <u>Dosing Compliance</u> Descriptive statistics will be used to summarize test article compliance for the Safety, ITT, and PP populations. Measures of test article compliance will</p>
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include the duration of treatment, the total number of applications (determined from the doses reported by the subject), and the percent of expected doses applied. A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of expected applications.

Local Skin Reactions

The frequency distributions of the severity scores of the LSRs associated with topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, folliculitis, and edema will be summarized by treatment group at Baseline, Day 8, and Day 15 for the Safety population.

Adverse Events

All subjects enrolled in the study who were dispensed and applied test article at least once (Safety population) will be included in the safety analyses based on adverse event reporting. 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 MedDRA mapping system. The PTs and SOCs will then be tabulated. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article by treatment.

Urine Pregnancy Testing

Results from the UPT at Screening/Baseline and Day 15 will be provided in a subject listing.

Amount of Test Article Applied

The total amount of test article used will be calculated from the weights of the returned test articles. Descriptive statistics will be provided by treatment group for the total amount of test article used by each subject for the Safety, ITT, and PP populations.

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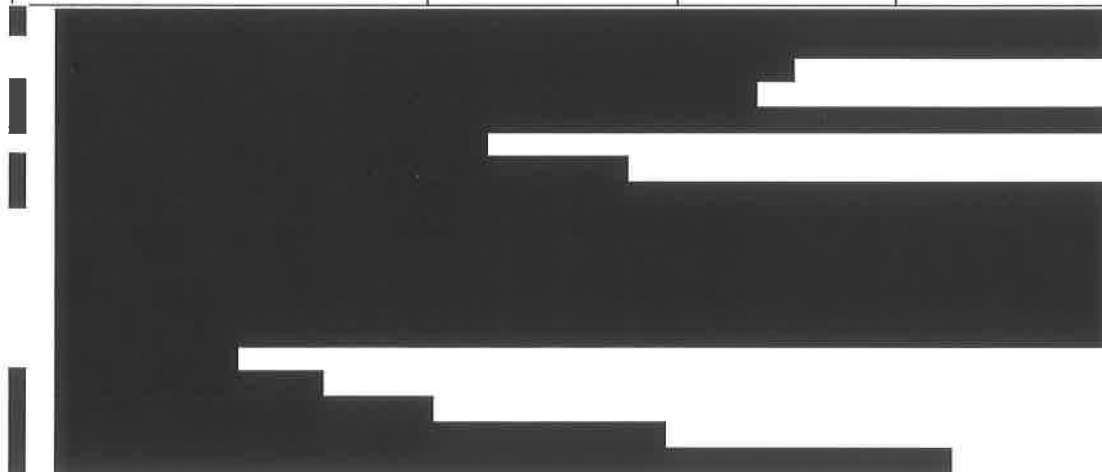
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SCHEDULE OF EVENTS

Study Day	Screening/Baseline ¹ Day 1 Visit 1	Week 1 Day 8 (± 2) Visit 2	Week 2 Day 15 (+ 3) ² Visit 3
Treatment	----- Twice Daily From Baseline to Day 15 -----		
Informed Consent	X		
Inclusion/Exclusion Criteria	X ³		
Urine Pregnancy Testing ⁴ for WOCBP ⁵	X		X
Medical History/Demographics	X		
Physical Exam - limited	X		
Clinical Evaluations (IGA, Clinical Signs, & Pruritus)	X (prior to test article application)	X ⁶	X
Record % BSA with active psoriasis in the Treatment Area (excludes the face, scalp, groin, axillae and other intertriginous areas)	X	X	X
Record Local Skin Reactions (LSRs)	X (prior to test article application)	X	X
Photography (selected study sites) ⁷	X	X (optional)	X
Randomization to treatment regimen (Subject # and ITA kit # assignment)	X		
Provide Instruction Sheet to Subject and demonstrate how to apply the test article ⁸	X		
Subject Diary	X (dispense)	X (collect & dispense)	X (collect)
Weigh/Dispense Test Articles	X	X	
Weigh/Collect Test Articles		X	X
Record Concomitant Medications	X	X	X
Record Adverse Events	X	X	X ⁹



ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
BSA	Body Surface Area
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HBP	Halobetasol Propionate
I/E	Inclusion/Exclusion
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITA	Investigational Test Article
ITT	Intent-to-Treat
IUD	Intrauterine Device
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
NF	National Formulary
ODS	Overall Disease Severity
OTC	Over-the-Counter
PP	Per-Protocol
PT	Preferred Term
QA	Quality Assurance
SAE	Serious Adverse Event
SD	Standard Deviation
SDA	Specially Denatured Alcohol
SOC	System Organ Class
TI	Therapeutics, Incorporated
UPT	Urine Pregnancy Test
USP	United States Pharmacopeia
VCA	Vasoconstrictor Assay
VEH	Vehicle
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

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1. BACKGROUND

[REDACTED]

[REDACTED]

[REDACTED]



2. RATIONALE

Super-potent topical corticosteroids are one of the mainstays of treatment for subjects with corticosteroid-responsive dermatoses such as psoriasis. The present Phase 3 study has been designed to determine and compare the efficacy and safety of HBP Foam and the VEH Foam applied twice daily for two weeks in subjects with plaque psoriasis.

3. OBJECTIVE

The primary objective of this study is to determine and compare the efficacy and safety of HBP Foam and the VEH Foam applied twice daily for two weeks (Study Day 15 + 3 days) in subjects with plaque psoriasis.

4. STUDY DESIGN

This is a Phase 3, double-blind, randomized, multicenter, vehicle-controlled, parallel group comparison study of HBP Foam and VEH Foam in adult subjects with plaque psoriasis. Approximately 400 subjects (200 per treatment group) with stable plaque psoriasis involving a minimum of 2% and no more than 12% BSA (excluding the face, scalp, groin, axillae and other intertriginous areas) who fulfill the inclusion/exclusion criteria will be enrolled at approximately 20 U.S. study sites. Subjects will be randomized in a 1:1 ratio to one of two treatment groups:

1. Halobetasol Propionate Foam, 0.05% (HBP Foam)
2. Halobetasol Propionate Foam Vehicle (VEH Foam)

All subjects will apply the assigned test article to all psoriasis plaques twice daily for 14 (+ 3) days.

5. STUDY POPULATION

The “Treatment Area” is defined as all areas of the body (excluding the face, scalp, groin, axillae, and other intertriginous areas).

To qualify for this study, per inclusion criterion #4, the subject must have a clinical diagnosis of stable plaque psoriasis involving 2 to 12% total body surface area (BSA) within the Treatment Area. See Section 10.4 for BSA calculation.

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 and is at least 18 years of age at the time of the Screening Visit.
2. Subject has provided written informed consent.
3. Subject is willing and able to apply the test article(s) as directed, comply with study instructions and commit to all follow-up visits for the duration of the study.
4. Subject has a clinical diagnosis of stable plaque psoriasis involving [REDACTED] body surface area (BSA)⁷ (excluding the face, scalp, groin, axillae and other intertriginous areas).
5. Subject has an Investigator's Global Assessment (IGA) score of at least three (3 = moderate) at the Baseline Visit.
6. Females must be post-menopausal⁸, surgically sterile⁹ or use an effective method of birth control^{10,11} with a negative urine pregnancy test (UPT)¹² at the Baseline Visit.

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.

⁷ 1% BSA is approximately equal to the surface area of the subject's palm and fingers, with the fingers extended yet grouped together, creating a flat oval-like surface area. For BSA determination residual discoloration (pigmentation and/or erythema) should not be included.

⁸ Defined as amenorrhea greater than 12 consecutive months in 55 years of age and older.

⁹ Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment) or bilateral oophorectomy.

¹⁰ Effective forms of birth control include hormonal contraceptives [oral, injectable, transdermal, or intravaginal] or intrauterine device (IUD) for two cycles (e.g., 8 weeks) (note: for Depo-Provera the requirement is at least 7 days after injection) 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 Women of childbearing potential (WOCBP) taking hormonal therapy must be on treatment for two cycles (e.g., 8 weeks) prior to study entry.

¹² UPTs must have a minimum sensitivity of 25 mIU β -hCG/mL.

3. Subject has a physical condition which, in the investigator's opinion, might impair evaluation of plaque psoriasis, or which exposes the subject to an unacceptable risk by study participation.
4. Subject has used any phototherapy (including laser), photo-chemotherapy, or other forms of photo based therapy for the treatment of their psoriasis within 30 days prior to the Baseline Visit.
5. Subject has used any systemic methotrexate, retinoids, systemic corticosteroids [including intralesional, intra-articular, and intramuscular corticosteroids], cyclosporine or analogous products within 90 days prior to the Baseline Visit.
6. Subject has used any systemic biologic therapy (i.e., FDA-approved or experimental therapy) within five (5) half-lives of the biologic prior to the Baseline Visit. Published or documented half-life of the product provided by the commercial supplier or Sponsor should be used to establish this value.
7. Subject had prolonged exposure to natural or artificial sources of ultraviolet radiation within 30 days prior to the Baseline Visit or is intending to have such exposure during the study which in the opinion of the investigator is thought to modify the subject's disease.
8. Subject has used topical body (excluding the scalp) psoriasis therapy (including coal tar, anthralin, steroids, retinoids, and vitamin D analogs) within 14 days prior to the Baseline Visit.
9. Subject has used emollients/moisturizers on areas to be treated within four hours prior to clinical evaluation at the Baseline Visit.
10. Subject is currently using lithium or Plaquenil (hydroxychloroquine).
11. Subject is currently using a beta-blocking medication (e.g., propranolol) or angiotensin converting enzyme (ACE) inhibitor at a dose that has not been stabilized, in the opinion of the investigator.
12. Subject has a history of sensitivity to corticosteroids or any of the ingredients in the test articles (see Section 6.1).
13. Subject is pregnant, lactating, or is planning to become pregnant during the study.
14. Subject is currently enrolled in an investigational drug or device study.
15. Subject has used an investigational drug or investigational device treatment within 30 days prior to the Baseline Visit.
16. Subject has been previously enrolled in this study and treated with a test article.
17. 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 13.2. Subjects who are discontinued will not be replaced.

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6. TEST ARTICLES AND REGIMEN

6.1 Description

Test article #1: **Halobetasol Propionate Foam 0.05%** [REDACTED]

Active ingredient: Halobetasol propionate

Other ingredients: [REDACTED]

Test Article #2: **Halobetasol Propionate Foam Vehicle (VEH Foam)**

6.2 Instructions for Use and Application

Subjects will apply the assigned test article (HBP Foam or VEH Foam) to all psoriatic plaques in the Treatment Area twice daily for two weeks.

Subjects will be provided with an instruction sheet (refer to Appendix 1) which includes detailed instructions for the application of test article.

The Treatment Area must be a minimum of 2% and no more than 12% BSA to fulfill study inclusion requirements. [REDACTED]

6.2.1 Test Article Application

At the Baseline Visit, 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 Treatment Area (as defined in Section 5).

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

Subjects should apply a thin uniform film of the assigned test article twice daily (morning and night) to all psoriatic plaques in the Treatment Area for two weeks (Study Day 15 + 3 days). The subject should ideally allow approximately eight hours or more separation between dose applications; not wash the treated area for at least four hours following test

article application, and should not apply the test article within four hours prior to any study visit. Areas that should NOT be treated under any circumstances include any areas of active psoriasis on the face, scalp, groin, axillae, or other intertriginous areas. Occlusion of treated areas is prohibited.

At each follow-up visit during the study, the investigator or designee should review proper application of the test article to all lesions designated for treatment.

As the subject's psoriatic plaques improve or worsen, the amount of test article applied will likely decrease or increase, respectively. Subjects with extensive disease which would typically require more than 50 grams of test article per week should not be enrolled in this study. If the subject's disease becomes unmanageable because of these limitations, they should be discontinued from the study as treatment failures.

The standard bland emollient provided for study use is ONLY to be used by the subject to treat those anatomic locations that are excluded from treatment (i.e., face, scalp, groin, axillae, or other intertriginous areas). The emollient may be applied to these areas as frequently as the subject desires to treat his/her psoriasis. An investigator-approved medicated (non-steroid) shampoo can be used to treat scalp psoriasis.

6.2.2 Treatment Duration

The subject will apply the test article to all psoriasis plaques twice daily for two weeks (Study Day 15 + 3 days).

6.3 Warnings, Precautions and Contraindications

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

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

Should skin irritation or rash develop, discontinue use.

Subjects should not occlude the treated areas.

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

The effects of halobetasol propionate in nursing mothers, pregnant women, and their unborn children are unknown. WOCBP must not be pregnant or planning a pregnancy during the study period.

7. RANDOMIZATION ASSIGNMENT

Subjects who are eligible for enrollment into the study will be randomized to receive HBP Foam or VEH Foam in a 1:1 ratio. The randomization scheme will be blocked by investigational site. At each site, subject kits (each containing three units) will be dispensed in ascending order as subjects are enrolled. At each site, the study staff will add the site number (provided to each site) and the subject number (starting with 001) to each kit label. The kit number dispensed to each subject will also be recorded on the source documents and CRFs. Treatment group designation will remain blinded until the final database is locked (unless unblinding is required as described in Section 15). Subject enrollment at the sites will be competitive. All subjects will apply the topical formulations as directed by the investigator.

8. PRIOR AND CONCOMITANT THERAPIES

Current medications and any medications taken in the 30 days prior to the start of the study (Screening/Baseline, Visit 1) will be recorded as prior/concomitant medications (using their trade names, if known) with the corresponding indication. The medications to be recorded include prescription and over-the-counter (OTC) medications (except vitamins and dietary supplements). All medications taken on a regular basis should be recorded on this page prior to commencing the use of the test article.

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health. Non-prohibited chronic therapies being used at Visit 1 may be continued. Any changes in concomitant therapies during the study must be recorded on the Concomitant Therapy form. The reason for any change in concomitant therapies should be evaluated and, if appropriate, reported as, or in conjunction with, an adverse event.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

above). The use of all such medication must be clearly documented in the subject's CRFs.

9. STUDY PROCEDURES

Specific activities for each study visit are listed below.

9.1 Visit 1 (Day 1): Screening/Baseline

At this visit, the investigator or designee will:

- Obtain a signed, written informed consent unless the subject signed a consent within the past 45 days.
- Complete review and documentation of the subject's medical history and demographic information.
- Record any concomitant medications and therapies.
- Confirm subject meets I/E criteria.
- Have subject complete washout from any prohibited medications, if necessary.
- Perform baseline activities of Visit 1 which should occur within 45 days of screening activities. For those subjects that required a washout period related to

- exclusionary medications, the investigator needs to reaffirm the subject meets all protocol requirements at Baseline.
- Perform a limited physical exam. The limited physical exam will include vital signs, height, weight, head and neck, pulmonary, cardiac and abdomen examinations, and an assessment of motor and gait function.
 - Perform a UPT for all WOCBP; the results must be negative for the subject to be enrolled into the study.
 - Identify the psoriatic plaques to receive treatment during the study. At this visit, the psoriatic plaques in the Treatment Area must include [REDACTED] BSA to fulfill study inclusion requirements. Lesions on the face, scalp, groin, axillae, and other intertriginous areas will not be included in the percent BSA calculation.
 - Record the location of the plaques to be treated with the test article in the CRFs.
 - Document the percent BSA with active psoriasis in the Treatment Area (see Section 10.4).
 - Perform Baseline clinical evaluations (IGA, clinical signs of psoriasis, and pruritus; see Section 10) prior to application of the test article.
 - Record Baseline LSRs prior to application of the test article.
 - Perform photography (selected study sites only; see Section 11).
 - If the subject meets the I/E criteria, randomize the subject by assigning lowest available study medication kit number in ascending order. At each site, the study staff will add the site number (provided to each site) and the subject number (starting with 001) to each kit label. The kit number dispensed to each subject will also be recorded on the source documents and CRFs.
 - Weigh and dispense initial canister(s) of test article.
 - Complete the Study Medication Accountability Log.
 - Dispense bland emollient provided, as required.

NOTE: The bland emollient is to be used only on non-diseased skin or diseased skin not being treated with the test article (i.e., the face, scalp, groin, axillae, and other intertriginous areas). Other emollients should be avoided during the trial except with the approval of the investigator to assure they are a bland emollient.

- Identify an investigator-approved, medicated (non-steroid) shampoo the subject will use for treating scalp psoriasis only, if appropriate.
- Dispense the Subject Instruction Sheet to the subject (Appendix 1). A body diagram may also be given to the subject to remind them where to apply (and where not to apply) the test articles. All psoriatic lesions in the Treatment Area must be treated with the test article.
- Dispense the Subject Diary (Appendix 2) to the subject and provide completion instructions.

- Have a study staff member instruct the subject where and how to apply the initial dose of test article following the procedures in Section 6.2.1. Subjects will apply the first dose of test article to all plaques under staff supervision in the clinic¹³.
- Instruct the subject to continue twice daily applications of the test article as instructed to all psoriatic plaques in the Treatment Area identified at this visit AND any new psoriatic lesions in the Treatment Area that may occur subsequently.
- Record any AEs.
- Schedule Visit 2 (Day 8 ± 2). Subjects should be instructed not to apply the test article within 4 hours prior to the scheduled clinic visit.

9.2 Visit 2 (Day 8 ± 2): Follow-Up

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 AE form as required.

- Review the subject's compliance with the study requirements, including twice daily application of test article as directed at Visit 1.
- Query the subject about any changes in concomitant medications/therapies (including the bland emollient and the investigator-approved medicated shampoo as appropriate) since the previous study visit and document the findings.
- Record LSRs associated with topical application of the test article (see Section 10.5).
- Perform photography, at the discretion of the investigator (selected study sites only; see Section 11).
- Perform clinical evaluations (IGA and clinical signs of psoriasis; see Section 10).
- Document the percent BSA with active psoriasis in the Treatment Area. This will include any remaining lesions identified at the Baseline Visit AND any new psoriatic lesions that may be present at this visit.
- Review subject instructions on the proper application of the test article (Appendix 1) as well as review (and discuss any discrepancies or concerns with the subject regarding their use of the diary), collect, and dispense another (new) Subject Diary (Appendix 2) and review completion instructions.
 - Instruct the subject to continue twice daily application of the test article as instructed to all psoriatic plaques in the Treatment Area.
- Collect and weigh used canisters of test article and weigh/dispense an additional canister of test article if necessary (see Appendix 4).
- Dispense bland emollient, as required.

¹³ Two applications of test article should be applied each day (approximately 8 hours or more separation between dose applications). If Visit 1 occurs in the late afternoon or evening, only one application will be possible on Day 1 and the time of this first application should be recorded on the Subject Diary (Appendix 2).

- Re-instruct the subject on the proper application of the test article and bland emollient. If necessary, to enhance compliance and proper application of the test article, the site may supervise test article application at this visit.
- Schedule Visit 3 (Day 15 + 3). Subjects should be instructed not to apply the test article within 4 hours prior to the scheduled final clinic visit.

9.3 Visit 3 (Day 15 + 3): Final Visit

These activities may occur as scheduled at the end of the treatment period or earlier if the subject is to be dropped from the study.

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 AE form as required.
- Review the subject's compliance with the study requirements.
- Query the subject about any changes in concomitant medications/therapies (including the bland emollient and the investigator-approved medicated shampoo as appropriate) since the previous study visit and document the findings.
- Record LSRs associated with topical application of the test article (see Section 10.5).
- Perform photography (selected study sites only; see Section 11).
- Perform clinical evaluations (IGA, clinical signs of psoriasis, and pruritus; see Section 10).
- Record the location of remaining plaques in the Treatment Area in the CRFs.
- Document the percent BSA with active psoriasis in the Treatment Area. This will include any remaining lesions identified at the Baseline Visit AND any new psoriatic lesions that may be present at this visit.
- Perform a UPT for all WOCBP.
- Collect and weigh all canisters of used/unused test article (see Appendix 4).
- Review the subject's diary for completeness of doses applied and times of application. Ask the subject if they applied the test article prior to the clinic visit.
- Discharge subject from the study.

10. CLINICAL EVALUATIONS

The following clinical evaluations will be performed per the schedules noted. The same expert grader should ideally complete the evaluations for a given subject throughout the study. If this is not possible (e.g., scheduling conflict, etc.), a different expert grader with overlapping experience with the subject and the study should complete the evaluations.

At Visit 1, the investigator will record the anatomical locations of the psoriatic plaques to be treated with the test article in the CRFs. The psoriatic plaques to be treated must include a minimum of 2% and no more than 12% BSA (see Section 10.4) excluding the face, scalp, groin, axillae, and other intertriginous areas. At the final visit, the investigator will record

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the anatomical locations of the remaining psoriatic plaques (excluding the face, scalp, groin, axillae, and other intertriginous areas) in the CRFs.

10.1 Investigator's Global Assessment (IGA)

The IGA score is a static evaluation of the overall or "average" degree of severity of a subject's disease, taking into account all of the subject's psoriatic lesions (excluding those on the face, scalp, groin, axillae, and other intertriginous areas) by the investigator or designee as the subject appears on the day of the evaluation. 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 degree of scaling, erythema, or plaque elevation that is present amongst all of the lesions eligible for treatment.

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 or a mathematical calculation based on the clinical signs of psoriasis scores. The Visit 1 assessment must be made PRIOR to the first application of the test article and subsequent assessments should be made four hours or more after any application of the test article. At every study visit, evaluate all active psoriasis plaques (excluding those on the face, scalp, groin, axillae and other intertriginous areas) and report the one whole integer score that describes the average IGA using the following scale:

Clear (0)	
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Almost Clear (1)	
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Mild (2)	
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Moderate (3)

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[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Severe (4)	
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

10.2 Clinical Signs of Psoriasis

This evaluation is a static assessment of the overall or “average” degree of severity of each of three key characteristics present within all of the subject’s psoriatic lesions in the Treatment Area (defined in Section 5) by the investigator or designee as the subject appears on the day of the evaluation. **The investigator should NOT refer to any other evaluations to assist with this assessment.** The Visit 1 assessment must be made PRIOR to the first application of the test article or bland emollient and subsequent assessments should be made four hours or more after any application of the test article. At every study visit, the investigator or designee will evaluate all psoriasis plaques in the Treatment Area and report the one whole integer score that describes the average severity for each clinical sign of psoriasis using the following scales:

Scaling:

0	Clear	No evidence of scaling.
1	Almost clear	[REDACTED]
2	Mild	[REDACTED]
3	Moderate	[REDACTED]
4	Severe	[REDACTED]

Erythema:

0	Clear	[REDACTED]
1	Almost clear	[REDACTED]
2	Mild	[REDACTED]
3	Moderate	[REDACTED]
4	Severe	[REDACTED]

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Plaque Elevation:

0	Clear	[REDACTED]
1	Almost clear	[REDACTED]
2	Mild	[REDACTED]
3	Moderate	[REDACTED]
4	Severe	[REDACTED]

10.3 Pruritus

The 5-D Pruritus Scale (7) will be used to assess the subjective and multidimensional experience of the subject's pruritus during the previous two weeks at Baseline and Day 15. Possible scores range from 5 (no pruritus) to 25 (most severe pruritus). The study staff should review the Pruritus Scale (see Appendix 3) with each subject and ask them to indicate the response that best describes their experience. The questionnaire should be completed by the subject at Visit 1, PRIOR to the first test article application and at Visit 3 (Day 15). Pruritus assessed by this evaluation should be reported as an AE only if therapy is required.

10.4 Percentage Body Surface Area with Active Psoriasis in the Treatment Area

The percent BSA with active psoriasis in the Treatment Area (Section 5) will be calculated and documented at all visits. The investigator may use the assumption that 1% BSA is approximately equal to the surface area of the subject's palm and fingers, with the fingers extended yet grouped together, creating a flat oval-like surface area. For BSA determination, residual discoloration (pigmentation and/or erythema) should not be included. The psoriatic lesions should involve [REDACTED] BSA at Baseline (see Section 5.1.1).

10.5 Local Skin Reactions (LSRs)

At every study visit, the investigator or designee will evaluate the severity (none, mild, moderate, or severe) of the following LSRs within the areas treated with test article known to be associated with topical application of corticosteroids:

- Telangiectasia
- Skin atrophy
- Burning/stinging
- Folliculitis
- Edema



12. LABORATORY TESTS

12.1 Urine Pregnancy Tests (UPTs)

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

13. END OF STUDY CRITERIA

At the end of each subject's participation in the study, the investigator will complete an End of Study form for all completed and discontinued subjects.

13.1 Completion of the Study

Subjects who complete the treatment as specified in the protocol will be considered to have completed the study. This includes the following:

- Any subject who completes 14 (+ 3) days of treatment and completes all of the Visit 3 evaluations.

13.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

- Whenever the subject decides it is in the subject's best interest to withdraw. NOTE: if the subject decides to withdraw from the study due to an AE then it should be classified as withdrawal due to an AE.
- Whenever the investigator decides it is in the subject's best interest to be withdrawn

- AEs
- 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

If a subject withdraws from the study prematurely for any reason, complete the final visit procedures. When a subject is withdrawn from the study for a treatment-related AE (i.e., possibly, probably or definitely related as defined in Section 14), when possible, the subject should be followed until resolution or stabilization of the AE.

Subjects who are prematurely withdrawn or discontinued from the study will not be replaced.

13.3 Study Termination

The study may be terminated by the investigator or the Sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, he or she may stop the study. A study termination by the investigator will be reported to the Sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the Sponsor by the investigator within five working days.

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

14. ADVERSE EVENT REPORTING

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

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with any drug) and from any route of administration, formulation or dose, including an overdose.

Information on the medical condition of subjects should begin following the subject's written consent to participate in the study and a medical history should be taken at screening. During any wash out and baseline periods, any changes in the health of subjects

should be recorded as changes in medical history unless an event occurred as a result of a study-related procedure and is unanticipated; in such cases, the event should be recorded as an AE and reported to the Institutional Review Board (IRB) 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 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).

14.1 Adverse Event (AE)

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

The investigator will instruct the subject to report any AEs that may occur during the study. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject’s overall condition since the previous visit.

The severity of each AE, as judged by the investigator, will be recorded on the appropriate AE CRF and will be graded according to the following scale:

Mild - The AE is transient and easily tolerated by the subject.

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

Severe - The AE causes considerable interference with the subject's usual activities, and may be incapacitating or life-threatening.

The investigator must determine the relationship of the AE to the test article according to the following categories:

Definite - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage, and reappearance of the event on repeated exposure (re-challenge).

Probable - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage of the test article; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.

Possible - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; but may have been caused by concurrent/underlying illness, other drug, procedure, or other causes.

Unlikely - An event that does not follow a reasonable temporal sequence from administration of the test article; that does not follow a known or expected response pattern to the test article, or most likely was caused by concurrent/underlying illness, other drug, procedure, or other causes, because of their known effects.

Not Related - An event almost certainly caused by concurrent/underlying illness, other drug, procedure, or other causes.

The investigator should categorize the outcome of the AE according to the following categories:

Fatal - Termination of life as a result of an AE.

Not Recovered/Not Resolved - AE has not improved or the subject has not recuperated.

Recovered/Resolved - AE has improved or the subject has recuperated.

Recovered/Resolved with Sequelae - subject recuperated but retained the pathological conditions resulting from the prior disease or injury.

Recovering/Resolving - AE is improving or the subject is recuperating.

Unknown - Not known, not observed, not recorded or subject refused.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. For the purposes of prescription drug labeling, the term adverse reaction means an undesirable effect, reasonably associated with the use of a drug that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

A **suspected adverse reaction** is any AE for which there is a reasonable possibility that the drug caused the event.

For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

14.2 Serious Adverse Event (SAE)

An event that is serious must be recorded on the AE CRF and on the TI SAE Report Form, and requires expeditious handling to comply with regulatory requirements.

An AE or suspected adverse reaction is considered "serious" if, in the opinion of either the investigator or Sponsor, it results in any of the following outcomes:

- Death.
- Life-threatening event.
- Inpatient hospitalization or prolongation of existing hospitalization.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Is an important medical event - defined as a medical event(s) that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events NOT considered to be serious AEs are:

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

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

Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In this case, the investigator must immediately report the event to the Sponsor. In addition, such information should also be provided to the site's respective IRB per their governing guidelines for SAE reporting.

If only limited information is initially available, follow-up reports are required. Should the investigator become aware of 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.

14.3 Pregnancy

WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea >12 consecutive months in women 55 years of age and older]. Even women who are using oral, implanted, or injectable contraceptive hormones, an IUD, barrier methods (diaphragm and spermicidal, condom and spermicidal) to prevent pregnancy, practicing abstinence, or where the partner is sterile (e.g., vasectomy performed at least six months prior to the subject's initiation of treatment) and the subject states she is in a monogamous relationship, should be considered to be of childbearing potential. Surgical means of sterilization (e.g., vasectomy, tubal ligation) must be a minimum of six months post-procedure to be considered effective birth control.

WOCBP must have a negative pregnancy test prior to study enrollment and must use an effective¹⁴ method of contraception during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors

¹⁴ Effective forms of birth control include hormonal contraceptives [oral, injectable, transdermal or intravaginal] or intrauterine device (IUD) for two cycles (e.g., 8 weeks) (note: for Depo-Provera the requirement is at least 7 days after injection) 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.

for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If a subject or investigator suspects that a subject may be pregnant at any time during the study the test article must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or apply further test article and must be discontinued from the study.

If following initiation of study treatment, it is subsequently discovered that a trial subject was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the Medical Monitor of this event, and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to 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 AE, any complications during pregnancy should be recorded as AEs (or SAEs – if they fulfill the SAE criteria). Offspring should be followed for a minimum of eight weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to the test article(s) should be recorded as a SAE and details documented in the pregnancy surveillance form. Abortion, whether accidental, therapeutic or spontaneous should be reported as a SAE.

15. BLINDING/UNBLINDING

This is a multicenter, randomized, double-blind, vehicle-controlled, parallel group comparison study of HBP Foam and VEH Foam. Blinding is important for the integrity of this clinical drug trial and all personnel involved with the clinical assessments of subjects must remain blinded with respect to the identity of the test articles dispensed to the subjects.

However, the blind may be broken in the event of a medical emergency in a subject, in which knowledge of the test article identity is critical to the subject's management. Before breaking the blind for a subject, the investigator should determine that the information is necessary (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not test article related, the problem may be effectively managed by assuming that the subject is receiving active product without the

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need for unblinding. The need to break the blind should first be discussed with the responsible Medical Monitor and the best method to do this will be determined.

16. CLINICAL SUPPLIES

16.1 Test Article Information

Test articles will be packaged and labeled by the Sponsor or designee. The identities of the products will be blinded prior to receipt by the sites. Detailed information on the packaging/labeling, blinding/unblinding, storage and preparation, dispensing, and accountability are included in Appendix 4.

16.2 Supplies Provided by Therapeutics, Inc.

- CRFs
- Site regulatory binder
- Bland emollient
- UPT kits
- Weighing scales for test articles (if necessary)

16.3 Supplies Provided by Investigator

- Urine collection containers
- Personal computer to store and view study photographs (designated study sites only)

17. STATISTICAL CONSIDERATIONS

17.1 Sample Size

A sample size of 200 subjects for each treatment group (i.e., HBP Foam and VEH Foam) is estimated to be sufficient to detect a true treatment difference of “success” rates [REDACTED] based on Fisher’s Exact Test with a power of 0.85 and a Type I error rate of 0.05 (two-tailed). [REDACTED]

Approximately 400 subjects are expected to be consented and enrolled into this study and assigned in a 1:1 randomization to one of two treatments: HBP Foam (200) and VEH Foam (200).

17.2 Endpoints

17.2.1 Efficacy Endpoints

IGA scores and the clinical signs of psoriasis will be dichotomized to “treatment success” or “treatment failure” where “treatment success” is defined as a score of 0 or 1 representing “cleared” or “almost cleared” with at least a two grade decrease in severity score relative to Baseline.

The primary efficacy endpoint will be the proportion of subjects with IGA “treatment success” at Day 15.

The key secondary efficacy endpoints are:

- The proportion of subjects rated a “treatment success” for plaque elevation at Day 15.
- The proportion of subjects rated a “treatment success” for scaling at Day 15.
- The proportion of subjects rated a “treatment success” for erythema at Day 15.

Other efficacy endpoints include:

- The proportion of subjects with IGA “treatment success” at Day 8.
- The proportion of subjects rated a “treatment success” for each of the clinical signs of psoriasis (scaling, erythema, and plaque elevation) at Day 8.
- Change from Baseline in pruritus score at Day 15.
- Changes in percent BSA with active psoriasis in the Treatment Area at Days 8 and 15.

17.2.2 Safety Endpoints

Safety endpoints will include assessment of LSRs associated with topical application of corticosteroids (telangiectasia, skin atrophy, burning/stinging, folliculitis, and edema), AEs, and SAEs.

17.3 Statistical Methods

All statistical processing will be performed using SAS[®] unless otherwise stated. Statistical significance for the primary efficacy endpoint will be based on a two-tailed test of the null hypothesis at the $\alpha=0.05$ level of significance.

Efficacy analyses will be performed primarily for the intent-to-treat (ITT) population. Efficacy analyses using the per-protocol (PP) population will be in support of the ITT analyses.

The Safety population will include all subjects enrolled in the study who were dispensed and applied test article at least once. Subjects will apply their first application of test article in the clinic during their Baseline Visit on Day 1. Subjects enrolled in the study who were

randomized and dispensed the test article will be considered the ITT population. Subjects will be included in the PP efficacy analyses if they have completed the study without significant protocol deviations. Subjects who discontinue from the study prematurely due to treatment failure, as determined by the investigator, will also be included in the PP population as treatment failures.

Demographic and baseline characteristics will be summarized by treatment group for the ITT, PP, and Safety populations. Frequency counts and percentages will be reported for categorical data and the number of subjects with non-missing data (n), mean, median, SD, minimum and maximum will be reported for the continuous variables.

17.3.1 Efficacy Analyses

17.3.1.1 Primary Efficacy Analysis

Efficacy will be demonstrated if the proportion of HBP Foam treated-subjects with IGA “treatment success” at Day 15 is statistically significantly greater than the proportion of VEH Foam-treated subjects that are “treatment successes” at Day 15 based on a two-sided test at the $\alpha=0.05$ level of significance. The treatment groups will be compared with respect to IGA treatment success rates at Day 15 using the CMH test stratified by center.

Subjects without data at Day 15 will be considered to be treatment failures (i.e., to not have achieved the primary endpoint). Note: this definition includes subjects who drop out of the study prior to Day 15 for any reason.

17.3.1.2 Key Secondary Efficacy Analyses

If the primary analysis is statistically significant ($p<0.05$), then a “gatekeeping” approach will be used to test the three key secondary endpoints:

- The proportion of subjects rated a “treatment success” for plaque elevation at Day 15.
- The proportion of subjects rated a “treatment success” for scaling at Day 15.
- The proportion of subjects rated a “treatment success” for erythema at Day 15.

Thus, if the analysis of the first key secondary endpoint is statistically significant at the $\alpha=0.05$ level of significance, then the second key secondary endpoint will be tested at the $\alpha=0.05$ level of significance. If this analysis is statistically significant, then the third key secondary endpoint will be tested at the $\alpha=0.05$ level of significance. However, if any previous analysis (including the primary analysis) is not statistically significant, all subsequent comparisons will be exploratory rather than confirmatory.

The treatment groups will be compared with respect to the proportions of subjects with “treatment success” for each of the signs of psoriasis at Day 15 using the CMH test stratified by center. Subjects with Baseline scores of 0 or 1 will be excluded unless the corresponding sign score at Day 15 is >1 .

17.3.1.3 Other Secondary Analyses

Investigator's Global Assessment (IGA)

The frequency distributions of IGA scores will be summarized by treatment group at Baseline, and at Days 8 and 15. The proportions of subjects considered a "treatment success" at Days 8 and 15 will be tabulated by treatment group. The treatment groups will be compared with respect to IGA treatment success rates at Day 8 using the CMH test stratified by center.

Clinical Signs of Psoriasis

The frequency distributions of the secondary efficacy endpoints, clinical signs of psoriasis (scaling, erythema, and plaque elevation), will be summarized by treatment group at Baseline, and at Days 8 and 15. The treatment groups will also be compared with respect to "treatment success" rates at Day 8 for each sign of psoriasis using the CMH test stratified by center. Subjects with Baseline scores of 0 or 1 will be excluded unless the corresponding sign score at Day 8 is >1 .

Pruritus

Descriptive statistics of the 5-D Pruritus Scale scores will be provided by treatment group at Baseline and at Day 15. The treatment groups will be compared with respect to the change from Baseline in pruritus score using analysis of covariance with the model including terms for treatment and center with the Baseline pruritus score serving as the covariate.

BSA with Active Psoriasis in the Treatment Area

The changes from Baseline in the percent BSA with active psoriasis in the Treatment Area will be summarized for each treatment group with descriptive statistics at Days 8 and 15.

17.3.2 Safety Analyses

Dosing Compliance

Descriptive statistics will be used to summarize test article compliance for the Safety, ITT, and PP populations. Measures of test article compliance will include the duration of treatment, the total number of applications (determined from the doses reported by the subject), and the percent of expected doses applied. A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of expected applications.

Local Skin Reactions

The frequency distributions of the severity scores of the LSRs associated with topical application of corticosteroids including telangiectasia, skin atrophy, burning/stinging, folliculitis, and edema will be summarized by treatment group at Baseline, Day 8, and Day 15 for the Safety population.

Adverse Events

All subjects enrolled in the study who were dispensed and applied test article at least once (Safety population) will be included in the safety analyses based on AE reporting. 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 SOCs using the MedDRA mapping system. The PTs and SOCs will then be tabulated. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article by treatment.

Urine Pregnancy Testing

Results from the UPT at Screening/Baseline and Day 15 will be provided in a subject listing.

Amount of Test Article Applied

The total amount of test article used will be calculated from the weights of the returned test articles. Descriptive statistics will be provided by treatment group for the total amount of test article used by each subject for the Safety, ITT, and PP populations.

17.4 Imputation of Missing Data

The primary efficacy endpoint is defined as a success rate. Any subject who cannot be confirmed as a “success” is a treatment failure; therefore, missing data is imputed as treatment failure.

The key secondary efficacy endpoints will be the proportion of subjects rated a “treatment success” for each of the clinical signs of psoriasis (scaling, erythema and plaque elevation) at Day 15. Subjects without data at Day 15 will be considered treatment failures, i.e., to not have achieved “treatment success”. Note that this definition includes subjects who drop out of the study prior to Day 15 for any reason.

17.5 Sensitivity Analyses

Sensitivity analyses will be performed to investigate the impact of data imputation on the primary endpoint (IGA “treatment success” at Day 15). These sensitivity analyses will include repeating the primary analysis (IGA “treatment success” at Day 15):

- 1) in the population of subjects with observed data for the primary endpoint (i.e., the “complete cases” population);
- 2) in the per-protocol population;
- 3) assuming that subjects with missing data are responders (“treatment success”);
- 4) assuming that subjects in the VEH Foam group with missing data are responders and that subjects in the HBP Foam group with missing data are treatment failures (“worst case”);
- 5) Using multiple imputation to impute missing values of the primary endpoint.

These analyses will be examined in conjunction with the reasons for dropout or the proportions of dropouts between treatment groups. Conclusions regarding the investigation of possible bias introduced by dropouts and/or the method of missing data imputation will be included in the final clinical study report.

For the sensitivity analysis based on multiple imputation, missing values of the primary endpoint will be imputed using the logistic regression methodology of SAS procedure MI. The logistic regression model will include the following independent variables: treatment and plaque elevation as the covariate. A minimum of 10 imputed data sets will be generated for this analysis. The MIANALYZE procedure of SAS will be used to combine the results.

17.6 Multicenter Studies

Each center will conduct the clinical study under a common protocol. Consistency in study execution at each center will be emphasized. The study is to be conducted in such a manner as to have a minimum of eight ITT subjects enrolled in each of the HBP Foam and VEH Foam treatment groups at each center.

The exploratory analyses discussed in the remainder of this section will be conducted using only those centers with at least eight ITT subjects in each of the two treatment groups.

The consistency of treatment response across the centers will be analyzed using a Breslow-Day test to evaluate a treatment by center interaction in the analysis of the primary efficacy variable (IGA "treatment success"). If the Breslow-Day test is significant ($p \leq 0.10$), a sensitivity analysis that excludes centers with the extreme efficacy results will be performed to determine the robustness of the treatment effect. Otherwise, the data will be considered to be free of the impact of extreme centers.

Identification of an extreme center begins by analyzing all subsets that can be created by excluding one center. If one or more of the subsets result in a Breslow-Day test for interaction p -value > 0.10 , then the center excluded from the subset with the largest p -value will be considered to be the extreme center.

If all of the subset p -values are ≤ 0.10 , the process will be repeated by excluding two centers. If one or more of these subsets result in an interaction p -value > 0.10 , then the centers excluded from the subset with the largest p -value will be considered to be the extreme center. This process is repeated until the p -value exceeds 0.10.

Upon identification of the extreme center(s), the analysis of IGA "treatment success" continues with the remaining centers. Inferences will be based on this analysis in addition to observations regarding the extreme center(s). Conclusions will be presented as appropriate to the findings of the sensitivity analysis.

17.7 Multiple Comparisons/Multiplicity

Statistical significance for the primary efficacy endpoint (IGA treatment success at Day 15) will be based on a two-tailed test of the null hypothesis of no difference at the $\alpha=0.05$ level of significance.

If the primary endpoint is statistically significant then the statistical significance testing for the three key secondary endpoints will use the “gatekeeping” approach (8) to control the overall level of significance.

Statistical significance testing for the other efficacy endpoints will be performed as supportive analyses for the primary and secondary endpoints and will not be adjusted for multiplicity concerns.

17.8 Subgroup Analyses

Treatment success rates (IGA) will be evaluated for subgroups based on gender (male/female), race (Caucasian/non-Caucasian) and age ($<65 / \geq 65$). Treatment success rates (IGA) will be evaluated for subgroups based on gender (male/female), race (Caucasian/non-Caucasian) and age ($<65 / \geq 65$).

17.9 Interim Analyses

No interim analyses will be performed.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Compliance with Good Clinical Research Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice 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 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 prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their assigned responsibilities.

18.2 Institutional Review Board (IRB) and Informed Consent

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the product labeling, information to be provided to subjects and any updates. The investigator will submit documentation of the IRB approval to Therapeutics, Inc.

The IRB-approved consent 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 must indicate voluntary consent by signing and dating the approved informed consent form. The investigator must provide the subject with a copy of the consent form, in a language the subject understands.

The investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

18.3 Protocol Compliance

The IRB-approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

18.4 Protocol Revisions

TI 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 TI.

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

18.5 Study Monitoring

Representatives of 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 TI of any audits of this study by any regulatory agency, and must promptly provide copies of any audit reports.

18.6 Case Report Form (CRF) Requirements

The study will utilize validated 21CFR Part 11 compliant EDC software to collect data. All requested information must be entered on the eCRFs in the areas provided in a timely manner. When changes or corrections are made in the eCRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change and the reason for the change. Only individuals listed on the Delegation of Responsibilities Log with responsibility for eCRF completion may make entries on the eCRFs. Usernames and passwords will be provided to each authorized user to allow access to the training module. Access to additional features and functions will not be enabled until the user upon receipt of EDC training documentation.

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

18.7 Reports to Institutional Review Board

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

18.8 Quality Assurance Audits (if not addressed in Agreements or Contracts)

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

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

18.9 Records Retention

All study records should be retained for a period of at least two (2) 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 (2) years after the investigation is discontinued and the FDA is notified.

The investigator must obtain TI approval in writing 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 TI.

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

18.10 Record Confidentiality

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

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

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IND: 107,302

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APPENDIX 1 SAMPLE SUBJECT INSTRUCTION SHEET

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

The investigator, or designee, should provide a copy of the Subject Instruction Sheet to each subject at Visit 1 (Day 1, Baseline Visit) and review these instructions at each study visit with the subject.

A body diagram may also be given to the subject by the study staff to remind them where to apply (and where not to apply) the test articles. A sample body diagram is included on the back of the Subject Instruction Sheet.

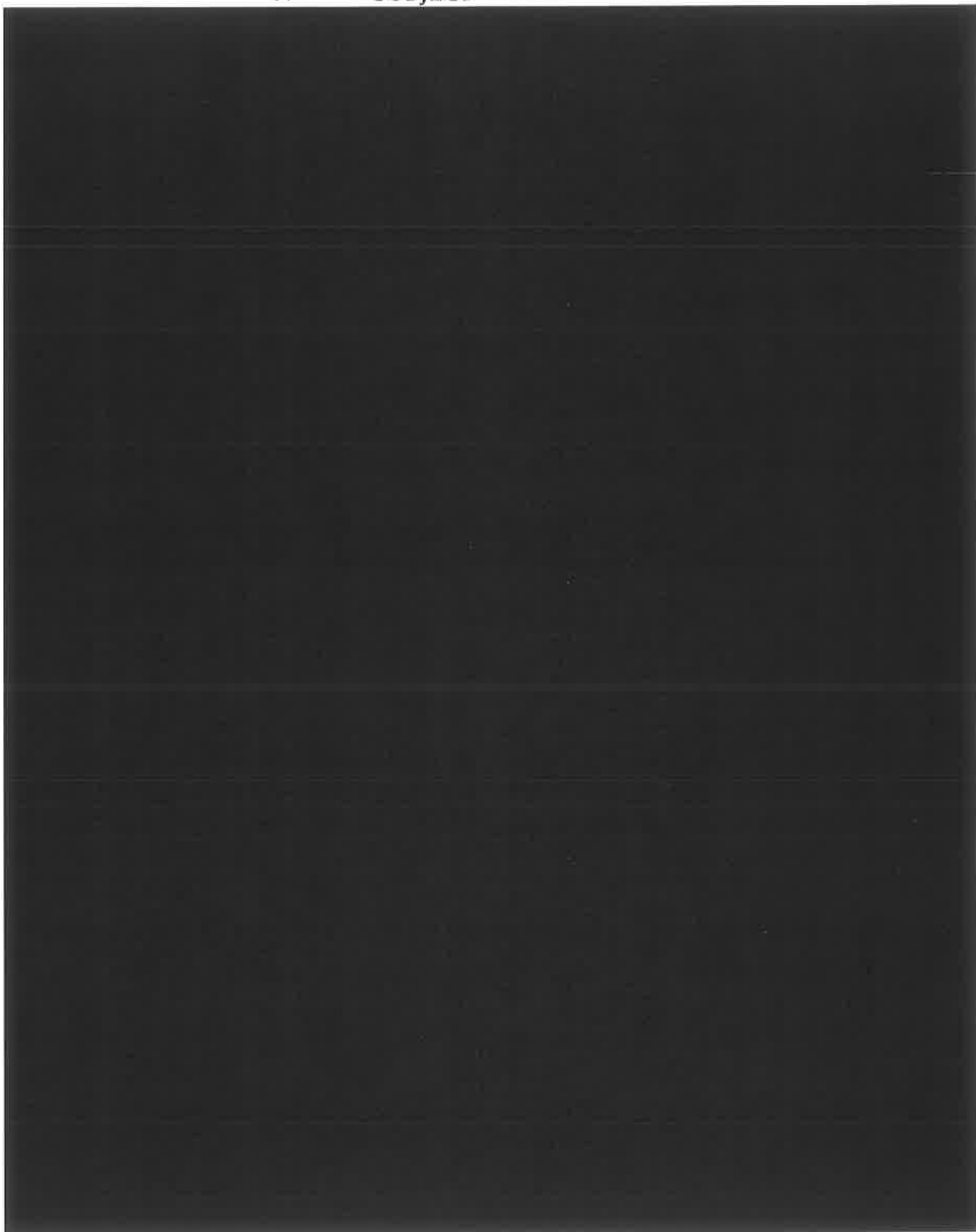
Product Name: Halobetasol Propionate Foam, 0.05%

IND: 107,302

Sponsor Name: [REDACTED]

Protocol: 122-0551-310; v2.0

SAMPLE SUBJECT INSTRUCTION SHEET



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Product Name: Halobetasol Propionate Foam, 0.05%

IND: 107,302

Sponsor Name: [REDACTED]

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[REDACTED]

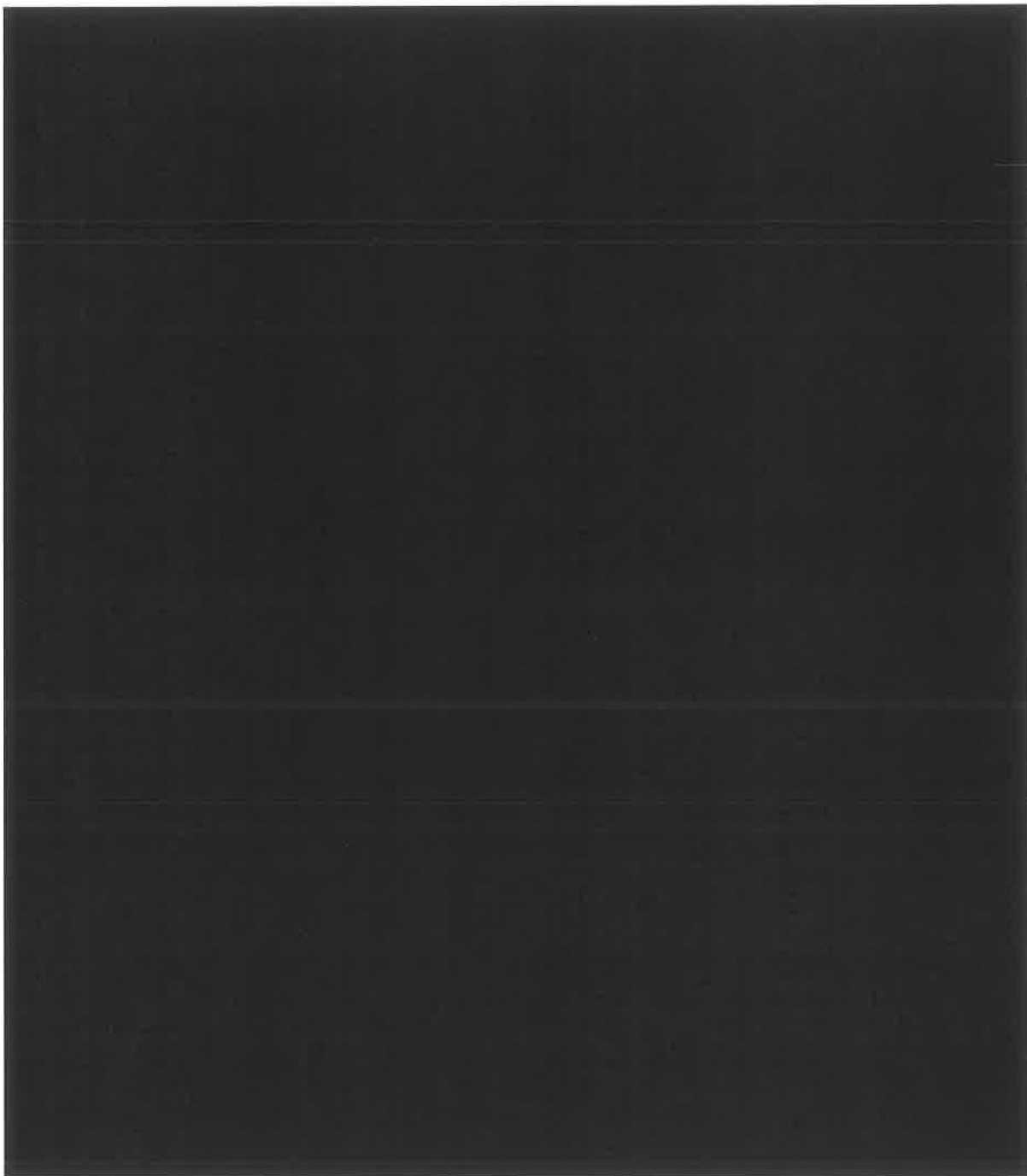
Product Name: Halobetasol Propionate Foam, 0.05%

IND: 107,302

Sponsor Name: [REDACTED]

Protocol: 122-0551-310; v2.0

BACK OF INSTRUCTION SHEET:



Product Name: Halobetasol Propionate Foam, 0.05%

IND: 107,302

Sponsor Name: [REDACTED]

Protocol: 122-0551-310; v2.0

APPENDIX 2 SAMPLE SUBJECT DIARY

A copy of the Subject Diary will be provided to each study site. The investigator should provide a copy of the Subject Diary to each subject at Visit 1 (Day 1, Baseline) and Visit 2 (Day 8, Follow-Up).

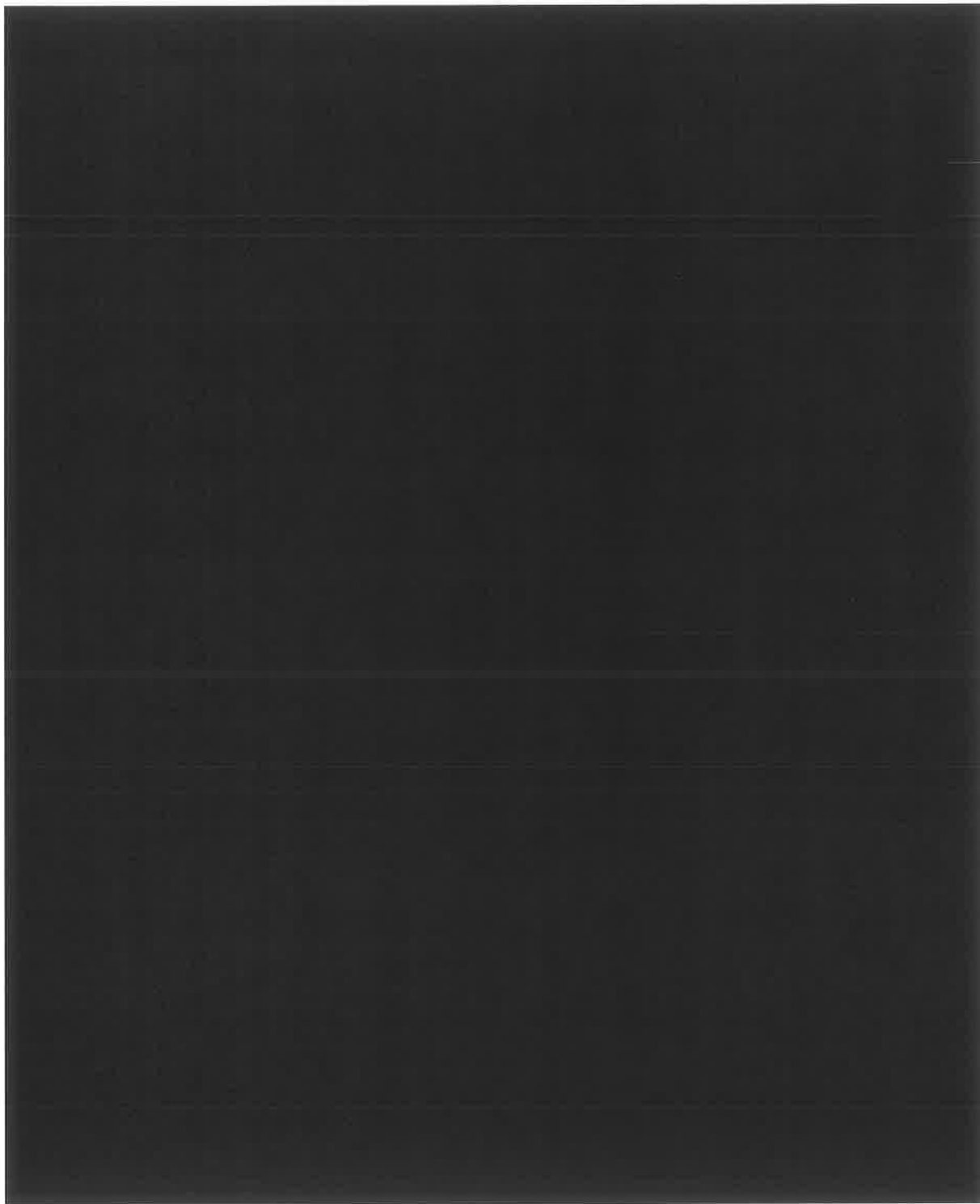
Product Name: Halobetasol Propionate Foam, 0.05%

IND: 107,302

Sponsor Name: [REDACTED]

Protocol: 122-0551-310; v2.0

SAMPLE SUBJECT DIARY for PROTOCOL 122-0551-310



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Product Name: Halobetasol Propionate Foam, 0.05%

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Sponsor Name: [REDACTED]

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APPENDIX 3 PRURITUS SCALE

Copies of the “5-D Pruritus Scale” on the next page will be provided to each study site.

The investigator should provide a copy of the pruritus scale to subjects at Baseline and Day 15 to determine their experience with pruritus during the previous 2 weeks.

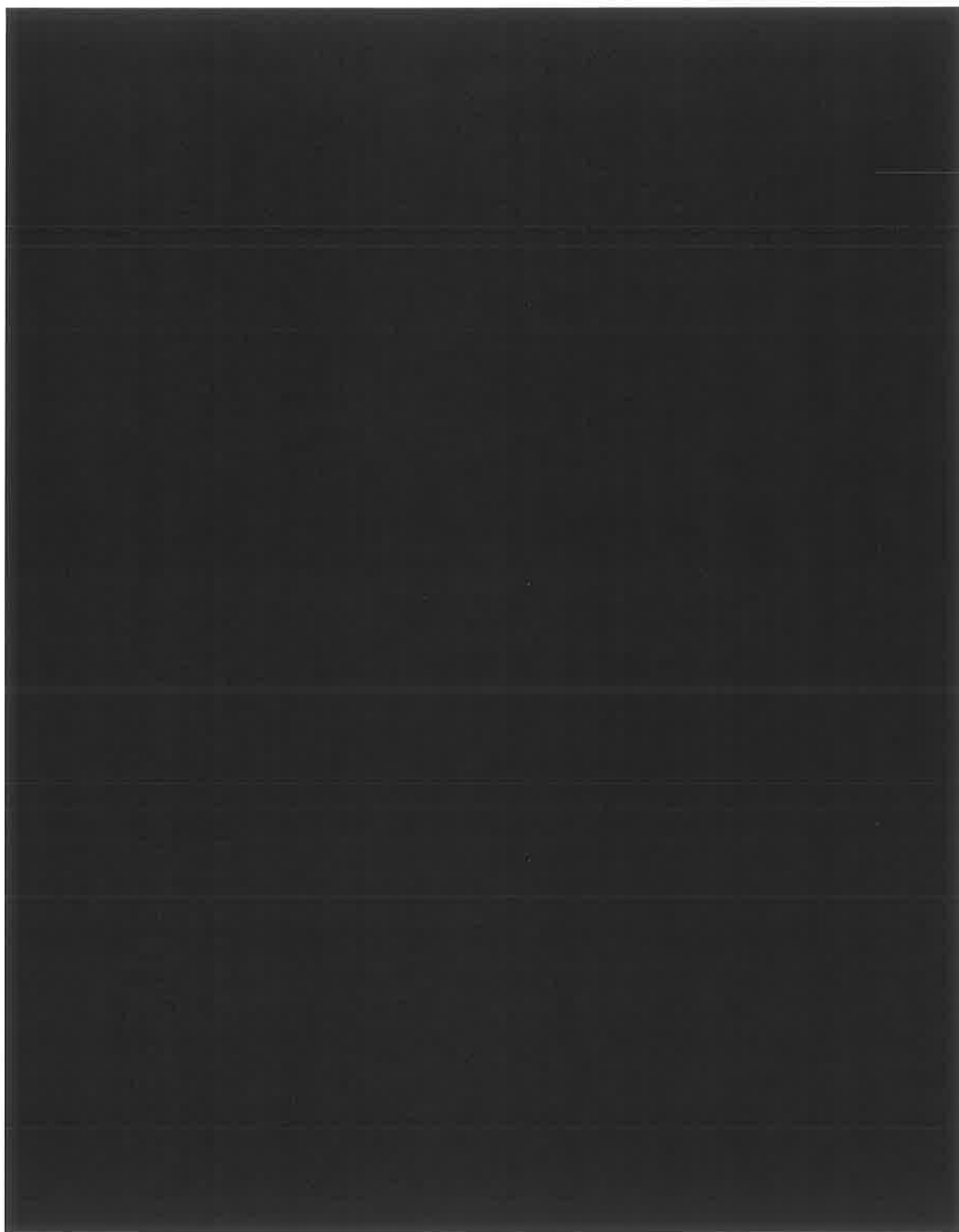
Product Name: Halobetasol Propionate Foam, 0.05%

IND: 107,302

Sponsor Name: [REDACTED]

Protocol: 122-0551-310; v2.0

5-D Pruritus Scale



Product Name: Halobetasol Propionate Foam, 0.05%

IND: 107,302

Sponsor Name: [REDACTED]

Protocol: 122-0551-310; v2.0

APPENDIX 4 TEST ARTICLE INFORMATION

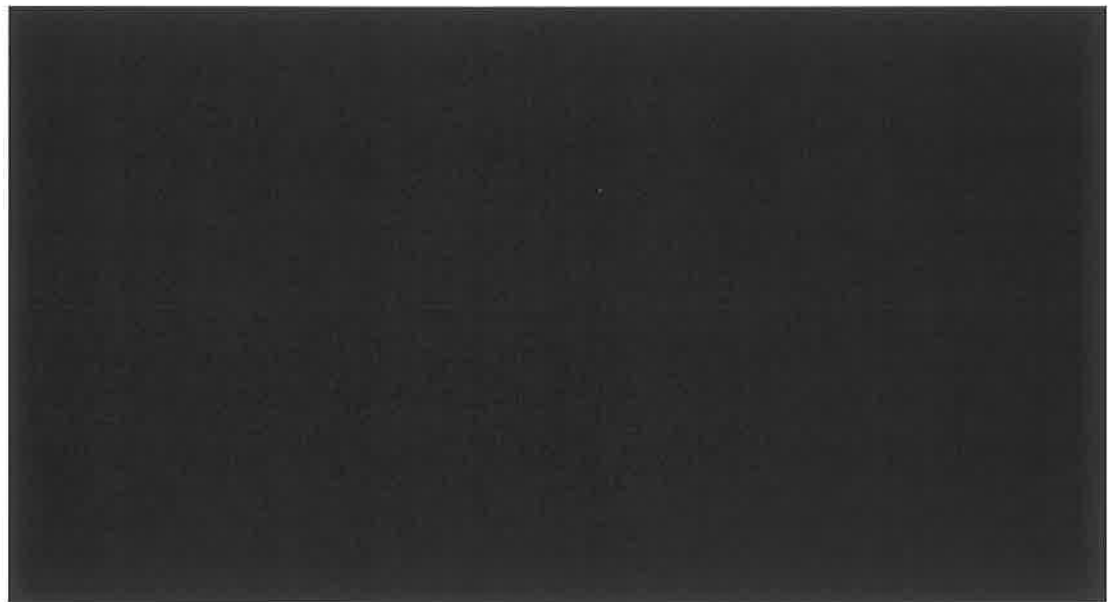
A 4.1 Test Article Packaging and Labeling

HBP Foam and Vehicle Foam will be manufactured for Therapeutics, Inc. The test articles will be packaged and labeled in aluminum canisters containing approximately 55 grams of test article.

All test articles will be labeled and packaged in identical subject kits with a double-blind label such that the products cannot be distinguished from one another while maintained in the secondary packaging.

Canister Labeling

The HBP Foam and Vehicle Foam canisters will be labeled with the following information:



Subject Kits and Labels

The labeled canisters of test article for each subject will be packaged in a box (aka "Subject Kit"), specifically, **three** canisters of test article with tamper-evident seals will be enclosed in each Subject Kit. Each Subject Kit of test article will have a label that contains the following information:



Product Name: Halobetasol Propionate Foam, 0.05%

IND: 107,302

Sponsor Name: [REDACTED]

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A 4.2 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 4.3 Dispensing Test Article

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.

At each site, the Subject Kits will be dispensed in ascending order (lowest available kit number) as subjects are enrolled. The study staff will add the site number (provided to each site) and the subject number (starting with 001) to each Subject kit label. The kit number dispensed to each subject will also be recorded on the source documents and CRFs.

Each of the canisters (with the canister cap) will be weighed prior to dispensing and the weights will be recorded on the appropriate source document. Subjects should be instructed to only use the second canister if the first one is misplaced or lost. The third canister will be kept at the site and will only be used during the study in the event of loss, spillage, or damage to the other canisters. Subjects should not have more than two canisters of test article in their possession at any time.

The subject number, canister number, date dispensed and dispenser's initials for each canister dispensed should be recorded on the Study Medication Accountability Log when the test article is dispensed.

When the subject returns each canister of test article, the date of return and initials of the individual accepting the return for each empty or nearly empty canister of test article should be recorded on the same line of the Study Medication Accountability Log as the dispensing information. Every effort should be made to obtain the return of all dispensed canisters of test article. If these efforts fail, a detailed note of the reason for the failure should be recorded on the appropriate line of the Study Medication Accountability Log.

A 4.4 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 4.5 Dose Modifications

If any sign of test article intolerance occurs, the investigator may direct the subject to reduce the frequency of application by skipping a day or more of treatment. If irritation continues, or if the subject cannot return to twice-daily applications within approximately three days of reducing the application frequency, the subject should be removed from the study following the procedures in Section 13. Any medication intolerance should be recorded as an AE. **The subject should not modify the treatment regimen without consultation with the investigator.** All dose modifications must be reported on the Study Medication Compliance Form in the subject's CRFs.

A 4.6 Documentation of Application and Compliance

A Subject Diary will be used to report any changes in dosing from the twice-daily application required by the protocol (e.g., missed applications, investigator directed reduction in application frequency). The date of the last application of test article will be recorded on the End of Study Form.

A 4.7 Return and Destruction of Test Article Supplies

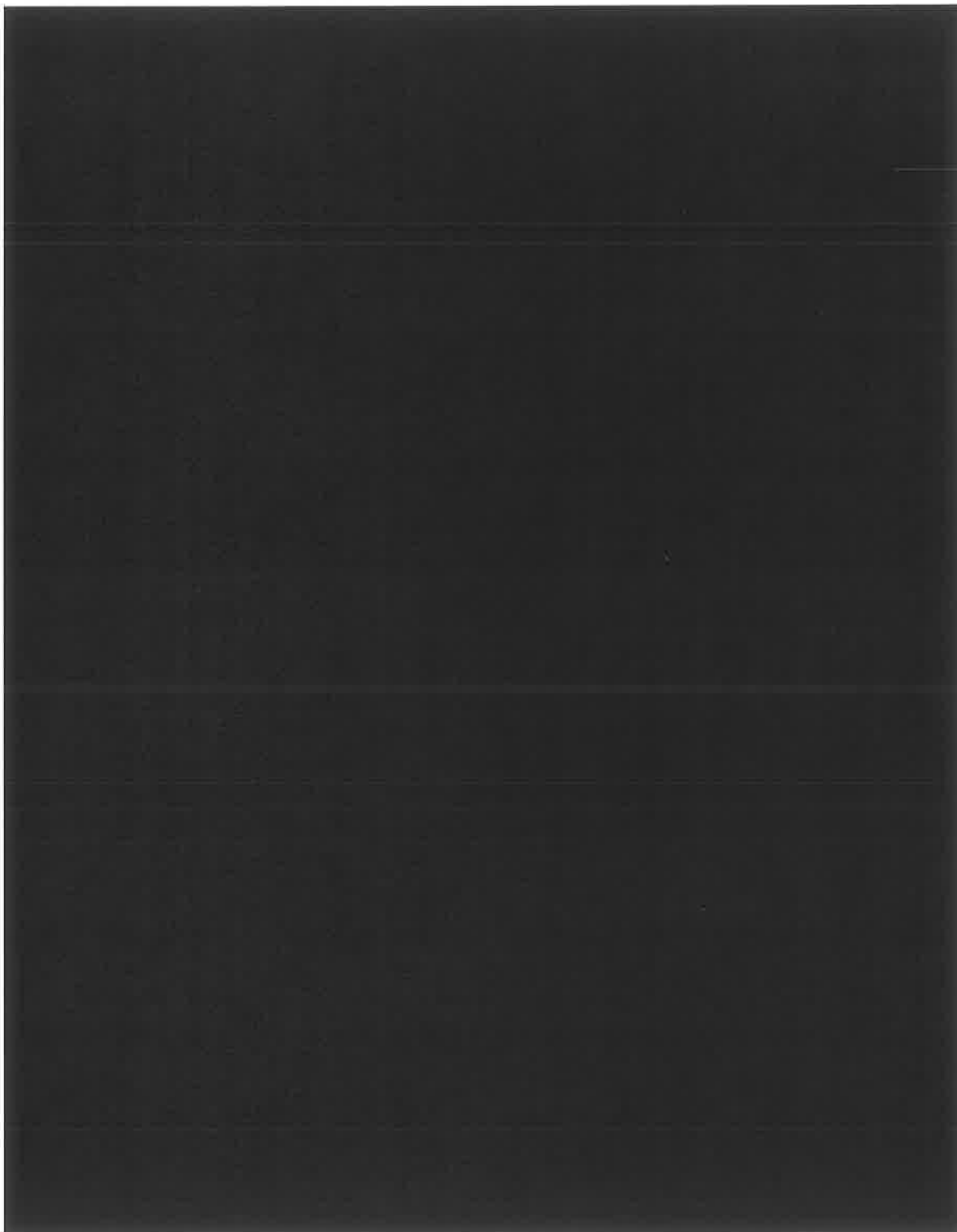
Upon completion or termination of the study, all test article canisters must be accounted for and any missing canisters of test article must be explained on the completed Study Medication Accountability Log. The study site must keep the original Label Pages and Study Medication Accountability Log in the study file. A photocopy of the Study Medication Accountability Log and Label Pages will be returned to the Sponsor.

All test article canisters will then either be: a) returned to the study Sponsor, or b) emptied and provided to a sponsor-identified third party vendor for appropriate destruction according to applicable regulations with the provision of a certificate of destruction.

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APPENDIX 5 PROTOCOL AMENDMENTS



Product Name: Halobetasol Propionate Foam, 0.05%
Sponsor Name: [REDACTED]

IND: 107,302
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