A double-blinded, placebo-controlled study to evaluate the tolerability and efficacy of Enstilar® (calcipotriene and betamethasone dipropionate) Foam in the treatment of chronic plaque psoriasis in patients with skin of color (Fitzpatrick skin phototypes IV-VI).

PI: Andrew Alexis, MD, MPH

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	Primary Contact Name/Contact Info:	Andrew Alexis, MD, MPH 212-523-3888
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HRP-503 PROTOCOL TEMPLATE

- *Note that, depending on the nature of your research, certain questions, directions, or entire sections below may not be applicable. Provide information if and when applicable, and in cases where an entire section is not applicable, indicate this by marking the section "N/A". Do not delete any sections.*
- ***For any items below that are already described in the sponsor's protocol, the investigator's protocol, the grant application, or other source documents, you may simply reference the title and page numbers of these documents in the sections below, rather than cutting and pasting into this document. Do not refer to the Sample Consent document, or information on the application form in this document.***
- *Keep an electronic copy of this version of the document. You will need to modify this copy when making changes.*

Brief Summary of Research:

Psoriasis is a chronic inflammatory disorder primarily affecting the skin and joints that occurs in diverse ethnic groups worldwide. There is paucity of data on the use of topical medications in dark-skinned individuals. Unique issues in skin of color (SOC) populations, including increased risk of dyspigmentation (hyperpigmentation and hypopigmentation), make studies dedicated to darker skin types essential for treatment of psoriasis in these populations.

This will be a single-center, randomized, double-blinded, vehicle-controlled clinical study to determine the efficacy of Enstilar® foam, a combination of calcipotriene and betamethasone dipropionate 0.005%/0.064%, in the treatment of psoriasis vulgaris in SOC (FST IV-VI). A total of 25 subjects (ages 18+, male and female, BSA ≥2%, PASI Score ≥ 2, IGA mod 2011 score ≥ 2) are expected to complete this study, which will run for a total of up to 12 weeks.

The study consists of three periods: Screening (from 0 to 4 weeks); Double-blind, vehicle-controlled treatment period (4 weeks), and open-label treatment period (4 weeks). During the second period (double-blind, vehicle-controlled), a total of 20 subjects will be randomized to Enstilar ® and a total of 5 subjects will be randomized to vehicle. Those who meet all of the inclusion/exclusion criteria and are enrolled in the study will receive study drug (either Enstilar® or vehicle) for the entire treatment period.

1) Objectives

The purpose of this study is to evaluate the efficacy and safety of combination calcipotriene and betamethasone dipropionate 0.005%/0.064% foam in the treatment of psoriasis vulgaris in males and females with skin of color (SOC).

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2) Background

Psoriasis is a chronic inflammatory disorder primarily affecting the skin and joints. This condition occurs in different ethnic groups worldwide with varying prevalence. In the United States, the Health and Nutrition Examination Survey estimated the prevalence of psoriasis to be 3.2% in adults; a significant number of affected were of darker phototypes, including African Americans (1.9%) and Hispanics (1.6%).[1,2] The true prevalence of psoriasis in black and Hispanic populations may actually be higher, given that non-whites are more likely to have undiagnosed psoriasis than whites (in part due to barriers to care and decreased health care utilization in these groups).[3,4]

Chronic plaque psoriasis classically presents as sharply demarcated erythematous plaques with micaceous scale. Nonetheless, there are notable differences in psoriasis presentation in skin of color groups. Black patients with psoriasis tend to have less erythema, increased risk of pigmentation, thicker plaques, more scaling, and greater body involvement as compared to white patients.[5,6,7] Several studies suggest that erythema is more challenging to detect in skin of color, and inflammation that typically manifests as pink or red lesions in lighter skin may appear violaceous or hyperpigmented in darker skin types.[8] The resolution of psoriasis lesions in darker skin types is associated with a higher rate of dyspigmentation (both hyper- and hypo-pigmentation), which may be more bothersome to patients than the psoriasis itself.[7,8]

Further, several studies have shown that psoriasis is associated with greater psychological impact and worse QOL in non-whites with psoriasis compared to whites.[5,8,9,10] Dermatology Life Quality Index (DLQI) scores are consistently lower in blacks and Hispanics compared to whites, even when controlling for body surface area affected and severity of disease.[10]

Despite differences in psoriasis between whites and non-whites, there is paucity of data on the use of topical medications in dark-skinned individuals.[11,12] Unique issues in SOC populations, including masking of erythema and high risk of post-inflammatory pigmentary sequelae, make studies dedicated to darker skin types essential for treatment of psoriasis in these populations.

Combination of calcipotriene and betamethasone dipropionate 0.005%/0.064% aerosol foam (Enstilar®) has been shown to be effective in the treatment of mild or greater plaque psoriasis when used once daily for 4 weeks.[13,14,15] Use of Enstilar ® has also been associated with significant improvement in health-related quality of life.[16] Nonetheless, pivotal phase II and III trials of Enstilar ® included a predominately white population; 87.1% of subjects in three pooled US phase II and III pivotal trials were white.[17] Given the small number of non-white subjects, it is difficult to make meaningful comparisons between different race/ethnicity subgroups.[17]

This will be a single-center, randomized, double-blinded, vehicle-controlled clinical study to determine the efficacy of Enstilar® foam, a combination of calcipotriene and betamethasone dipropionate 0.005%/0.064%, in the treatment of psoriasis vulgaris in SOC (FST IV-VI). This study will also evaluate the degree of erythema versus hyperpigmentation in psoriasis plaques in SOC (and its change with Enstilar ® treatment) as well as the effect of Enstilar ® on post-inflammatory hyperpigmentation and quality of life in SOC. [18]

3) Setting of the Human Research

All research activity will take place at Mount Sinai West Department of Dermatology, located at 2109 Broadway, 2nd Floor, New York, NY 10023.

4) Resources Available to Conduct the Human Research

The research team consists of the Principal Investigator, Sub-Investigator, and Research Coordinator(s). Dr. Alexis, Principal Investigator of this study and director of Mount Sinai St. Luke's and West Skin of Color Center, cares for a large number of SOC patients with psoriasis vulgaris. We therefore do not foresee any difficulties in recruiting the suggested number of patients for this research study. All members of the study team have several years of research experience and have all completed the required trainings and certifications mandated by our IRB. All research team members have read and understand the protocol and all study related procedures.

5) Study Design

a) Recruitment Methods

Subjects will be recruited from the dermatology faculty practices and the dermatology resident clinics in the Mount Sinai Health System. Once approved by the Sponsor, we will use IRB approved flyers, online advertisements (including social media postings and clinical trials listing services) as well as questionnaires and phone scripts.

b) Inclusion and Exclusion Criteria

Inclusion:

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1. Provide written, signed and dated informed consent prior to initiating any study-related activities.
2. Male or female >18 years of age at the time of screening
3. Fitzpatrick Skin phototype IV-VI, non-white race/ethnicity, including but not limited to African Americans, Asians, Pacific Islanders and Hispanics.
4. Clinical diagnosis of chronic plaque-type psoriasis of the body
5. Plaque psoriasis with ≥2% Body Surface Area (BSA) involvement (may include scalp involvement), PASI Score ≥ 2, IGA mod 2011 score of 2 or greater (based on scale of 0-4)
6. Females of childbearing potential (FCBP) must have a negative pregnancy test at Screening and Baseline. While using investigational product and for at least 28 days after last application of investigational product, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options described below:

   Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy;

   OR

   Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]; PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

7. Must be in general good health as judged by the Investigator, based on medical history and physical examination. (NOTE: The definition of good health means a subject does not have uncontrolled significant co-morbid conditions).

Exclusion:

1. Form of diagnosed psoriasis other than chronic plaque psoriasis (i.e. guttate, erythrodermic, pustular)
2. Diagnosis of other active, ongoing skin diseases or skin infections that may interfere with examination of psoriasis lesions

3. Ongoing use of other psoriasis treatment including but not limited to topical or systemic corticosteroids, other topical medications (i.e. coal tar), oral or biologic medications for the treatment of psoriasis, and UV therapy. The following washout periods will be required:
    - 2 weeks for topical therapy
    - 2 weeks for phototherapy
    - 12 weeks for biologic or targeted therapies
    - 4 weeks for other systemic therapies
4. Use of oral estrogen therapy, excluding oral contraceptive pills
5. Women who are pregnant, nursing, or of child-bearing potential who are unwilling to use appropriate method(s) of contraception.
6. Patients unwilling to limit exposure to UV light
7. Current significant medical problems that, in the discretion of the investigator, would put the patient at significant risk
8. Patients with disorders of calcium metabolism and/or hypercalcemia.
9. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamics half-lives, if known (whichever is longer).
10. History of allergy to any component of the IP

c) Number of Subjects

Patients with skin types IV-VI with chronic plaque-type psoriasis will be screened with a goal of 25 total subjects randomized. All 25 randomized subjects are expected to complete all study procedures. Individuals who provide informed consent and fail to meet all of the inclusion and exclusion criteria during the initial evaluation will be considered a "screening failure."

d) Study Timelines

The study will consist of 6 visits over up to 12 weeks (up to 4 week screening period plus 8 weeks enrolled in study). Study visits will be conducted at Screening (Visit 1), Baseline (Visit 2, Week 0), Week 1 (Visit 3), Week 2 (Visit 4), Week 4 (Visit 5), and Week 8/discontinuation (Visit 6).

Enrollment will occur over a 6 month period from November 2017 to May 2018.

e) Endpoints

Primary Endpoint:

1. **Investigator Global Assessment (IGA mod 2011) at week 4**
   Proportion of patients at week 4 who achieved treatment success according to investigator global assessment (IGA mod 2011) of the entire body including scalp. IGA will range from 0 (clear) to 4 (severe). Treatment success is defined as IGA of clear (0) or almost clear (1) for patients with ≥ moderate disease at baseline or IGA of clear (0) for patients with mild disease at baseline.

Secondary Endpoints:

1. **Psoriasis Area and Severity Index 50 and 75 (PASI50 and PASI75) at weeks 2, 4, and 8.**
   Proportion of patients achieving ≥50% improvement and/or ≥75% improvement in Psoriasis Area and Severity Index (PASI) at weeks 4 and 8 compared to baseline (PASI 50 and PASI 75, respectively). PASI will be completed by the investigator or trained qualified designee at screening and weeks 0, 2, 4, and 8.

2. **Psoriasis Scalp Severity Index 50 and 75 (PSSI50 and PSSI75) at weeks 2, 4 and 8, if applicable**
   Proportion of patients achieving ≥50% improvement and/or ≥75% improvement in Psoriasis Scalp Severity Index (PSSI) at weeks 4 and 8 compared to baseline (PSSI 50 and PSSI 75, respectively), if applicable. PSSI will be completed by the investigator or trained qualified designee at screening and weeks 0, 2, 4, and 8 if the subject has/had scalp involvement at the baseline visit.

3. **Investigator Global Assessment (IGA mod 2011) at weeks 2 and 8**
   Proportion of patients at week 8 who achieved treatment success according to investigator global assessment (IGA mod 2011) of the entire body including scalp. IGA will range from 0 (clear) to 4 (severe). Treatment success is defined as IGA of clear (0) or almost clear (1) for patients with ≥ moderate disease at baseline or IGA of clear (0) for patients with mild disease at baseline.

4. **Scalp Investigator Global Assessment (ScIGA) at weeks 4 and 8, if applicable**

Proportion of patients at weeks 4 and 8 who achieved treatment success according to scalp investigator global assessment (ScIGA). ScIGA will range from 0 (clear) to 4 (severe). Treatment success is defined as ScIGA of clear (0) or almost clear (1) for patients with ≥ moderate disease at baseline or ScIGA of clear (0) for patients with mild disease at baseline.

5. **Patient's Global Assessment of Itch at weeks 1, 2, 4, and 8**

   The VAS is a numerical scale used to assess patients' perception of pruritus/itch. Subjects will be asked to complete the VAS scale at all scheduled visits. The evaluation is a 10cm long line on which the subjects indicate the severity of their pruritus from "0" (no pruritus) to "10" (severe pruritus).

6. **Patient's Global Assessment of disease severity (PaGA) at weeks 4 and 8. Treatment success will be defined as clear or almost clear**

   At weeks 4 and 8, subjects will be asked to assess the severity of their psoriasis on a PaGA patient questionnaire. PaGA will have 5 distinct options ranging from "Clear" to "Severe." Treatment response will be defined as clear or almost clear disease (for those with moderate or severe disease at baseline) or clear disease (for those with mild disease at baseline).

7. **Change in erythema index of target psoriasis plaque from baseline to weeks 2, 4, and 8**

   A skin spectrophotometer (Mexameter) will be used to quantify the degree of erythema of lesional skin compared to an index area (of unaffected skin) at baseline, week 2, week 4, and week 8. Erythema index will be recorded at these timepoints and compared to baseline measurements.

8. **Change in melanin indices of target psoriasis plaque from baseline to weeks 2, 4, and 8**

   A skin spectrophotometer (Mexameter) will be used to quantify the melanin index (degree of hyperpigmentation or hypopigmentation) of lesional skin compared to an index area of unaffected skin)at baseline, week 2, week 4, and week 8. Melanin index will be recorded at these timepoints and compared to baseline measurements.

9. **Change in physician dyspigmentation visual analog scale (VAS) at weeks 4 and 8.**

   An investigator will perform a visual analog scale (VAS) rating the degree of dyspigmentation of the skin. This VAS will range from - 5 to 5 as follows: 5 severe dark

brown pigmentation (darkest imaginable color), 4 dark brown pigmentation, 3 medium brown pigmentation, 2 light brown pigmentation, 1 slight dark pigmentation (barely perceptible compared to surrounding skin), 0 baseline skin pigmentation, -1 slight hypopigmentation (barely perceptible compared to surrounding skin), -2 mild hypopigmentation (light brown), -3 moderate hypopigmentation (creme-colored skin), -4 severe hypopigmentation (almost complete absence of pigment), -5 depigmentation (complete absence of pigment). This VAS will be performed at baseline and weeks 4 and 8.

10. **Change from baseline in Dermatology Life Quality Index (DLQI) total score at weeks 2, 4 and 8.**

Subjects will complete a DLQI at baseline, week 2, week 4 and week 8. Change in DLQI total score between baseline and week 4 will be assessed.

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a) Procedures Involved in the Human Research

Table 1: Assessment Schedule

Visit	1	2	3	4	5	6
Week	-4 to BL	0 (BL)	1	2	4	8 ET/EOT
Visit Window (days)			±2	±2	±5	±5
Assessment						
Informed Consent	X					
Demographics	X					
Inclusion/Exclusion	X	X				
Medical History	X					
Psoriasis treatment history	X					
AE/SAE assessment	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Vital Signs	X					
Height and Weight	X					
Physical Examination	X					
Fitzpatrick Skin Type assessment	X					
Photography		X			X	X
Urine Pregnancy Test	X	X				
BSA	X	X		X	X	X
Investigator IGA mod 2011 score (and ScIGA if applicable)	X	X		X	X	X
PASI score (PSSI if applicable)	X	X		X	X	X
Mexameter measurement of erythema and melanin indices		X		X	X	X
Investigator dyspigmentation VAS		X			X	X
Patient Global Assessment of severity (PaGA)		X		X	X	X
Patient pruritus VAS		X	X	X	X	X
Patient dyspigmentation VAS		X			X	X
Dermatology Life Quality Index (DLQI)		X		X	X	X
Local Tolerability Assessment		X	X	X	X	X
Treatment satisfaction evaluation				X	X	X
Study Drug Training		X				
Study Drug Dispensation and Return		X			X	X

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This is a single-center study and will consist of 3 phases. Phase 1 - screening phase, Phase 2 - Double-blinded, vehicle-controlled phase, and Phase 3 - Open-label and maintenance phase

Phase 1 - The screening phase will last up to 28 days. Screening and baseline may occur on the same day if subject does not require a wash-out period.

Phase 2 - double-blinded, placebo-controlled phase to evaluate the tolerability and efficacy of Enstilar® (calcipotriene and betamethasone dipropionate) Foam versus placebo in the treatment of chronic plaque psoriasis in patients with skin of color (Fitzpatrick skin phototypes IV-VI). This phase will last 4 weeks (baseline to week 4). Subjects will be randomized in a 4:1ratio to Enstilar® or placebo, respectively. The study product will be applied once daily for 4 weeks.

Phase 3 - Open-label and maintenance phase. Subjects who were randomized to placebo during phase 2 will receive Enstilar daily x 4 weeks. Subjects who were randomized to Enstilar during phase 2 will switch to Enstilar twice weekly x 4 weeks as maintenance treatment.

Prior to the start of the study, potential subjects will be given an IRB-approved Informed Consent Document (ICD) containing a Health Insurance Portability and Accountability Act (HIPAA) disclosure agreement to read, understand, and sign. After providing informed consent, subjects will be assessed for study eligibility at the Screening visit. The PI or a medically qualified designee must review this information (i.e. medical history, concomitant medication, and eligibility review) for each subject to confirm their eligibility before enrollment.

A total of 25 subjects who meet eligibility criteria will undergo Baseline / Day 0 assessments. At this Baseline visit, subjects will undergo randomization to either active drug or vehicle. All subjects will receive study drug training. Study drug will be dispensed at baseline and week 4. Un-used drug will be returned to the site at each visit.

Subjects will return for visits at weeks 1, 2, 4, and 8 so that a review of concomitant medications and adverse events can be assessed. The PI or designee will interview the subjects to collect and record any adverse events (AEs) or changes to health/concomitant medications that may have occurred since the previous visit. Additional procedures and assessments will be performed as outlined in table 1.

If a subject terminates early or chooses to discontinue the study, he/she will be asked to return for a final visit, at which time the procedures for visit 6 will be performed.

Enstilar ® foam is a combination of calcipotriene 0.005%, a vitamin D analog, and betamethasone diproprionate 0.064%, a corticosteroid. Enstilar ® foam is indicated the treatment of plaque psoriasis in patients 18 years of age and older.

During phase 2 of the study, the study product (Enstilar ® foam or vehicle) should be applied topically to affected areas of the skin once daily. During phase 3, frequency of Enstilar ® is dependent on treatment group. Those randomized to Enstilar ® during phase 2 will start a maintenance regimen: twice weekly application of Enstilar ® for 4 weeks. Those randomized to vehicle during phase 2 will start the treatment regimen: once daily application of Enstilar ® for 4 weeks.

The procedures and assessment performed during this study are described in detail below:

Informed Consent: Prior to the start of the study, potential subjects will be given an IRB-approved Informed Consent Document (ICD) containing a Health Insurance Portability and Accountability Act (HIPAA) disclosure agreement to read, understand, and sign. All questions about the study should be answered to the satisfaction of the candidate subject. They will have all of their study-related questions answered by the PI or designee, and if they agree to participate, the subject will sign the ICD. The subjects will retain one original copy and one photocopy will be kept in the study file. The subjects who sign an ICD will be assigned a screening number.

Demographics: Subjects will be asked to complete a questionnaire about their demographics at the screening visit. This will include date of birth, sex, race, and ethnicity.

Eligibility Assessment (Inclusion/Exclusion): After providing informed consent, subjects will be assessed for study eligibility at the Screening visit, which includes limited physical examination, skin type assessment, vital signs, height and weight, investigator severity ratings (PASI, PGA, PSSI and PScIGA if applicable), review of medical history and concomitant medications as well as prior medications/treatments, and urine pregnancy test (if applicable). These assessments will be described below. The PI or a medically qualified designee must review this information (i.e. medical history, concomitant medication, and eligibility review) for each subject to confirm their eligibility before enrollment. Eligibility will be assessed at Screening and Baseline visits.

Medical History and Concomitant Medications: At the screening visit, subjects will be asked about current medical conditions or history of any medical conditions. Subjects will also be asked about current medication use and use of medications for 1 month prior to screening. Concomitant medications will be reviewed and recorded at every scheduled visit.

Psoriasis Treatment History: At the screening visit, subjects will be asked about their current and all past treatments for psoriasis, including over-the-counter and prescription therapies.

Vital Signs: Vital signs will be assessed at the screening visit. Whether action needs to be taken regarding abnormal vital signs (as defined below) will be at the investigator's discretion. After the

subject has been sitting for at least five minutes with back supported and both feet on the ground, systolic and diastolic blood pressure (BP) will be measured using an appropriately sized cuff. Pulse will also be measured using either an automated machine or manually. Normal Blood pressure will be defined as systolic 90 to <120mmHg and diastolic 60 to <80mm Hg. Notable blood pressure will be hypertension (systolic ≥140 mmHg and/or diastolic ≥100 mmHg). A normal pulse rate will be defined as 60 to 100 beats per minute. Notable pulse rates will be defined as bradycardia (<50bpm) and tachycardia (>100bpm).

Height and Weight: Height and weight will be measured by a designated site individual at the screening visit.

Physical examination: Physical examination will be performed by the investigator, sub-investigator, or other qualified individuals at screening. This will include examination of the heart, lungs, abdomen, extremities, and skin, as well as any additional body systems as deemed necessary by the investigator.

Photography: Standardized photographs will be taken of the entire body (front and back). The photograph will be taken with the patient standing up in front of a neutral background; photographs will be taken at a standardized distance with the patient facing towards and away from the camera such that the entire body included in the picture. Photographs will be taken at baseline and weeks 4 and 8.

Body Surface Area (BSA): The total body involvement of psoriasis will be recorded as a percentage of the totally BSA at screening, baseline, and weeks 2, 4, and 8.

Investigator's Global Assessment (IGA mod 2011): The IGA mod 2011 is a standardized rating scale for assessment of overall psoriatic disease severity. IGA mod 2011 (entire body including scalp) will be performed by the investigator or designated qualified site staff at screening, baseline, and weeks 2, 4, and 8. If the subject has scalp involvement at the baseline visit, Scalp IGA (ScIGA) will be performed. For ScIGA, the IGA mod 2011 scale will be used to evaluate the severity of psoriasis on the scalp only.

The scale is as follows:

Score	Short Description	Detailed Description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions

Psoriasis Area and Severity Index (PASI) (and Psoriasis Scalp Severity Index (PSSI) if applicable)

The investigator or trained qualified site staff will complete the PASI (and PSSI assessment) at screening, baseline, and weeks 2, 4, and 8.
When calculating the PASI score, four separate body regions are evaluated: the head (including face, scalp, and neck), upper limbs, trunk (including axillae and groin area), and lower extremities (including the buttocks). These body regions correspond to 10%, 20%, 30%, and 40% of the total body surface area (BSA), respectively. Therefore, the score for each body region will be multiplied by its relative proportion of the body surface area (0.1, 0.2, 0.3, or 0.4) when calculating the PASI score.
Three different parameters will be evaluated: erythema (E), desquamation (D), and induration (I). These will be graded on a scale of 0 (none) to 4 (very severe). Desquamation refers to the scaling of a lesion. Induration refers to the thickening and plaque elevation.

PASI is calculated based on the following formula:
$$\mathbf{PASI = 0.1(E_H+I_H+D_H)A_H + 0.2(E_U+I_U+D_U)A_U + 0.3(E_T+I_T+D_T)A_T + 0.4(E_L+I_L+D_L)A_L}$$

PASI Scoring System:

Body Region	Erythema (E)	Induration (I)	Desquamation(D)	Area Score (A)
Head (H)	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0– no involvement 1– >0 to <10% 2– 10 to <30% 3– 30 to <50% 4– 50 to <70% 5– 70 to <90% 6– 90 to 100%
Trunk (T)	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0– no involvement 1– >0 to <10% 2– 10 to <30% 3– 30 to <50% 4– 50 to <70% 5– 70 to <90% 6– 90 to 100%
Upper Extremities (U)	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0– no involvement 1– >0 to <10% 2– 10 to <30% 3– 30 to <50% 4– 50 to <70% 5– 70 to <90% 6– 90 to 100%
Lower Extremities (L)	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0 – none 1– slight 2 – moderate 3– severe 4 – very severe	0– no involvement 1– >0 to <10% 2– 10 to <30% 3– 30 to <50% 4– 50 to <70% 5– 70 to <90% 6– 90 to 100%

When calculating PSSI, similar grading of erythema (E), induration (I), and desquamation (D) will be performed with a scale of 0 (none) to very severe (4). In addition, the extent of scalp involvement (0 to 100%) will be assessed. The area score will graded in the same manner as the PASI score (1– >0 to <10%, 2– 10 to <30%, 3– 30 to <50%, 4– 50 to <70%, 5– 70 to <90%, 6– 90 to 100%). For those with no scalp involvement (0) at baseline, PSSI will not be performed.

PSSI score = $(E_s+I_s+D_s)A_s$

Patient Global Assessment of severity (PaGA):
Patient will complete a PaGA questionnaire at baseline, week 2, week 4, and week 8 to ask about severity of their overall clinical condition. The scale will include 5 categorical options – clear, very mild, mild, moderate, and severe.

Short Description	Detailed Description
Clear	No signs of psoriasis at all
Very Mild	Very slight psoriasis symptoms that do not interfere with daily life at all
Mild	Slight psoriasis symptoms that only occasionally interfere with daily life
Moderate	Definite psoriasis symptoms that frequently interfere with daily life
Severe	Intense psoriasis symptoms that very often interfere with or restrict daily life

Subject VAS of pruritus: The VAS is a numerical scale used to assess patients' perception of pruritus/itch. Subjects will be asked to complete the VAS scale at baseline and weeks 1, 2, 4, and 8. The evaluation is scored from 0 (no pruritus) to 10 (severe pruritus).

Dermatology Life Quality Index (DLQI): DLQI is a validated 10-question questionnaire developed to address quality of life in patients with dermatological disorders. It has previously been used with success to assess the impact of psoriasis on quality of life. Patients will be asked to fill out a DLQI at baseline, week 2, week 4, and week 8.

Patient Satisfaction Questionnaire: Subjects will be asked to complete a questionnaire asking about satisfaction with the study product, including satisfaction with the product vehicle, ease of application, and overall satisfaction with the treatment product.

Local Tolerability Assessment: Assessment of local safety and tolerability will be completed at baseline and weeks 1, 2, 4, and 8. The investigator or designated site staff will assess for: perilesional erythema, edema, dryness, and erosion. These parameters will be graded on a scale of 0 (absent) to 3 (severe). The subjects will also be asked about application site burning and pain after application of the study drug. Subjects will be asked to grade their burning/stinging from 0 (absent) to 3 (severe). Only severe site reactions or reactions that require discontinuation of the study product will be recorded as AEs.

Urine Pregnancy test: Urine pregnancy test will be performed at screening and baseline visits for women of child-bearing potential. A woman is considered post-menopausal if she has not had a menstrual period in >12 months.

Adverse Events and Serious Adverse Events: An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition this should be considered an AE. All AEs will be recorded by the Investigator(s) from the time of signing the informed consent through the end of the designated follow-up period.

b) Specimen Banking

N/A

c) Data Management and Confidentiality

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial. All subject source documents are the site's subject records and are to be maintained at the study site. These source documents must be attributable, legible, contemporaneous, original, and accurate.

A CRF/source document is required and should be completed for each included subject. It is the PI's responsibility to ensure completion and to review and approve all CRFs/source documents. These must be signed by the PI or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs/source documents is true. At all times, the PI has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs/source documents. SAE forms and pregnancy notification forms will be provided by the Sponsor.

Good documentation practices should be used on all study documentation. The clinical study will be performed in accordance with the protocol, applicable standard operating procedures (SOPs), the International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines, and applicable local regulatory requirements and laws.

The Sponsor requires that all records (e.g., ICFs, source documents, test article dispensing record, etc.) which support CRFs/source documentation of this study must be retained in the files of the responsible investigator for a period of 2 years from the time the final report is issued.

If the investigator relocates, retires, or for any reason withdraws from the trial, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met. The Sponsor must be notified in writing of the name and address of the new custodian prior to re-assignment/transfer.

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Only the subject number will be recorded in the CRF. The code that links the subject to the subject's ID# is stored on paper in a locked cabinet, accessible only by Department of Dermatology research personnel. Photographs will be stored on the camera for approximately one week before being transferred to the computer database. Study findings stored on a password-protected computer will be encrypted and stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subject's identity will remain confidential. Only the investigator will maintain a list to enable subjects to be identified. The data will be stored indefinitely.

d) Provisions to Monitor the Data to Ensure the Safety of Subjects

Part I: Elements of a Data and Safety Monitoring Plan

MSSM Principal Monitor:
Indicate whether this person is the PI, a Team Member, or is Independent:
Last Name: Alexis (PI)

First Name: Andrew
Academic Title: MD, MPH
Department: Dermatology
Mailing Address: [redacted], New York NY 10025
Phone: 212-523-3888
Fax: 212-523-3808
E-mail: aalexis@chpnet.org

2. The principal monitor is the Principal Investigator. Please refer to curriculum vitae for further information.
3. The specific items that will be monitored for safety are pregnancy, adverse events, subject compliance with the protocol and drop outs.
4. Subjects will be monitored for adverse events the day of their participation in the study. Should subjects experience any adverse effects after their participation in the study, they will be instructed to contact the investigator(s) and make an appointment immediately.
5. The investigator(s) will not change the Clinical Study Protocol without written approval of the IRB.
6. N/A
7. Adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE).
8. The study will be conducted in compliance with regulatory requirements and Good Clinical Practice. Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.
9. Should a temporary or permanent suspension of our study occur, the occurrence will be reported to the PPHS, sponsor, and IRB.

Part II. Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB)

N/A

e) Withdrawal of Subjects

When an individual who has signed the ICF is not enrolled in the study or withdraws/is withdrawn prior to completing the study, the reason is to be documented on the Discontinuation/Completion Form (or equivalent) and in the final study report. Reasons for subject withdrawal may include:

- Not enrolled (e.g. fails to meet inclusion/exclusion criteria, chooses not to enroll, etc.)
- Participant is determined to be ineligible after enrollment
- Subject's choice to withdraw
- Investigator terminated (e.g. noncompliance, etc.)
- Adverse Event
- Lost to follow-up
- Other

Subjects may withdraw from the trial at any time at their request, or they may be withdrawn at any time at the discretion of the Sponsor, PI, or designee for safety, behavioral, or administrative reasons. Subjects may be withdrawn from this study without their consent if the research study is being stopped; or if the instructions of the study team have not been followed.
If a subject does not return for a scheduled visit, *three documented attempts will be made to contact the subject in order to establish the reason for withdrawal, and* the outcome will be documented. The PI or designee should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

Should a subject withdraw from the trial and also withdraw consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The PI and staff may retain and continue to use any data collected before such withdrawal of consent. Removed or withdrawn subjects will not be replaced.

If a subject fails to report to the test facility for a scheduled visit and cannot be rescheduled within the permitted window of time (as applicable), the Site should consult with the Sponsor to determine if the subject should be documented as having withdrawn/dropped from the study.

2) Risks to Subjects

The following list of side effects is the ones that may be associated with the use of Enstilar ® foam:

Observed in less than 1% of subjects (based on clinical trials):

- Application site reactions:
  - Irritation
  - Pruritus
- Folliculitis
- Skin hypopigmentation

- Hypercalcemia
- Urticaria
- Exacerbation of psoriasis

Observed uncommon adverse reactions (based on post-marketing data):

- Atrophy of thin skin
- Telangiectasia of the skin
- Dryness of the skin
- Perioral dermatitis
- Secondary infections of the skin
- Miliaria

Other warnings:

- **Hypercalcemia and hypercalciuria –** Hypercalcemia and hypercalciuria have been observed with the use of Enstilar ® foam. If either of these conditions develop, Enstilar ® should be discontinued until calcium levels normalize in the blood and/or urine.
- **Endocrine system effects –** The systemic absorption of topical corticosteroids may lead to reversible suppression of the hypothalamic-pituitary-adrenal (HPA) axis, which may result in clinical glucocorticoid insufficiency either during treatment or upon withdrawal of the topical steroid. The risk of HPA axis suppression is higher with use of high-potency steroids, treatment of a large surface area, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age.
- **Allergic contact dermatitis** – Topical calcipotriene and topical corticosteroids have both been associated with allergic contact dermatitis.
- **Risk of ultraviolet light exposure** – patients would have using Enstilar ® foam should avoid excessive exposure to natural and artificial sunlight (i.e. tanning booths, sun lamps)
- **Flammability** – The propellants in Enstilar ® foam are flammable. Subjects should avoid smoking, flames, and fire during and immediately following Enstilar ® application.

Enstilar ® foam is designated as pregnancy category C, meaning that there are no adequate and well controlled studies in pregnant women. Studies of calcipotriene administered orally in rats and rabbits have demonstrated increased maternal and fetal toxicity at doses above 144 mcg/m2/day (rabbits) and skeletal abnormalities at dosages above 432 mcg/m2/day in rabbits and 324 mcg/m2 /day in rats. These are lower than the estimated maximum topical dose of calcipotriene in humans (460mcg/m2/day).

Betamethasone propionate has been shown to be teratogenic in mice and rabbits when given subcutaneously at dosages of 468 mcg/m2 /day (mice) and 30 mcg/m2 /day (rabbits). Again, these levels are lower than the estimated maximum topical dose in humans (~5,950mcg/m2/day).

When administered systemically, corticosteroids have been shown to enter human milk and can have negative effects on infant health. Possible risks of systemic corticosteroids on infants include growth suppression and altered production of endogenous steroids. It is not known whether topically administered calcipotriene and/or corticosteroids results in sufficient systemic absorption to produce detectable quantities of these medications in human milk. Enstilar ®, therefore, should not be used by women while breastfeeding.

3) Provisions for Research Related Harm/Injury

If a subject experiences a research injury, Mount Sinai St. Luke's will provide or arrange for medical treatment at no cost. If the subject chooses to see their own personal doctor we will not offer to pay for the expenses. A research injury is any physical injury or illness caused by participation in the study. If a subject is injured by a medical treatment or procedure that would have been received even if the subject weren't in the study; that is not a research injury. Payment for things such as lost wages, expenses other than medical care, or pain and suffering is not offered. To help avoid injury, it is very important to follow all study directions.

Please be aware that some insurance plans may not pay for research-related injuries. Subjects should contact their insurance company for more information.

4) Potential Benefits to Subjects

The potential benefits to participating subjects are improvement of their psoriasis.

5) Provisions to Protect the Privacy Interests of Subjects

Only subjects who have given us permission to contact them for studies will be contacted. All conversations with subjects and potential subjects will be conducted in a private examination room with the subject. Subjects' privacy will be protected by performing any study-related procedures in a private examination room. Family members will be allowed to remain in the room only if the subject allows this. No information regarding the subject's disease, treatment or the fact that he/she is involved in a study will be conveyed.

Subjects will be made to feel at ease, by allowing them sufficient time to discuss the study and any potential queries.

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The ICD (containing the HIPAA disclosure agreement) must be agreed to by the IRB and be in compliance and consistent with ICH GCP, local regulatory requirements, and legal requirements.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the trial, possible risks associated with participation. The investigator, or a trained person designated by the investigator, will obtain written informed consent on two copies from each subject before any trial-specific activity is performed. The subject will retain one copy, and one will be kept in the study file. The ICD used in this trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB and Sponsor before use.

6) Economic Impact on Subjects

Leo Pharma, the manufacturer of the study drug, will provide the study drug. Leo Pharma also provided a grant toward study-related tests and procedures. While in the study, the subject will still need to get regular medical care. The subject will still have to pay for the costs of regular medical care that is not a part of this study.

Taking part in this research study may lead to added costs to the subject. If the physical examinations reveal information about his/her health, additional tests, treatments and doctors' appointments may be required which could present additional costs to him/her or his/her insurance company.

7) Payments to Subjects

Subjects will be compensated [redacted] upon completion of the study. Subjects who complete only the screening visit will not be eligible for compensation. If the subject withdraws or is withdrawn before completing the study, he/she will receive an amount of money for the visits which have been completed. They will not have to submit receipts to receive this reimbursement. This payment will come in the form of a check at the end of the subject's participation in the study.

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8) Consent Process

We will be obtaining written consent as a part of this study. No subject will be evaluated without a signed Informed Consent Document (ICD). The consent process will take place in a private exam room where the subject will have ample time to review and read the consent form. Subjects will be given time to ask questions and may take additional time to consider their options. Subjects will be informed that they do not have to participate and may withdraw consent at any time. After understanding and agreeing, the subject will express her consent to participate in the study by signing two original copies of the ICD. We will follow the SOP HRP-090 Informed Consent Process for Research

9) Process to Document Consent in Writing

We will be using the standard IRB Informed Consent template. The ICD must be agreed to by the Sponsor and the IRB and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The consent process and date that the consent is signed is documented in our source notes. Study personnel will adhere to "SOP HRP-091 Written Documentation of Consent".

10) Vulnerable Populations

Indicate specifically whether you will include (target) or exclude each of the following populations:

Include	*Exclude*	*Vulnerable Population Type*
	x	*Adults unable to consent*
	x	*Individuals who are not yet adults (e.g. infants, children, teenagers)*
	x	*Wards of the State (e.g. foster children)*
	x	*Pregnant women*
	x	*Prisoners*

11) Multi-Site Human Research (Coordinating Center)

N/A

12) Community-Based Participatory Research

N/A

13) Sharing of Results with Subjects

At the completion of the study, subjects will have the right to access their protected health information that is created during this research study that relates to their treatment or to payment, provided such information is not exempted under certain laws and regulations. To request this information, subjects should contact the study doctor at the address listed above.

Subject to certain exceptions prescribed by law, subjects have a right to request access to the health information that we hold about and to request changes if the health information is incorrect or incomplete. Any request for access or corrections should be made to the principal doctor conducting this study.

14) External IRB Review History

N/A

15) Control of Drugs, Biologics, or Devices

Study drug is stored in a combination-locked room accessible only by clinical trials personnel. All study materials should be stored at room temperature (59°-77°F), and the Site is responsible for maintaining temperature logs. All study products received and dispensed will be inventoried and accounted for throughout the study. The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the products on the Product Accountability Log. The log must identify the investigational product and account for its disposition by subject, including specific dates and quantities dispensed and returned. The log must be signed by the individual who dispensed/retrieved the study product and copies must be provided to the sponsor for inclusion in the Trial Master File.

At the completion of the study, all units of product dispensed (whether empty or containing unused product) must be collected by the Site and returned, along with un-dispensed product, to the Sponsor. Any container not returned by the Site must be accounted for in writing.

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