1.0 TITLE PAGE

Drug Product	Desoximetasone 0.25% Shampoo
Population	Up to (370) patients (18 years of age or older) with mild to severe plaque psoriasis of the scalp
Study Design	A Randomized Double-Blind, Vehicle-Controlled, Parallel-Design, Multiple-Site, Phase III Clinical Study
Sponsor	Taro Pharmaceuticals U.S.A., Inc.
Protocol Number	DSXS 1536
Novum Study Number	71515013
IND #	124879
Protocol Date	02/10/2016
Rev 1 Date	02/24/2016
Rev 2 Date	05/31/2016

NIIRB
June 7, 2016
APPROVED

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2.0 KEY STUDY PERSONNEL AND FACILITIES

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SIGNATURE PAGE

We, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study. The study will be performed according to this protocol, all applicable FDA regulations, ICH guidelines and Good Clinical Practice standards.

Gail Gongas
Vice President, Clinical Trials
Novum Pharmaceutical Research Services

06/10/2016
Date

Paolo Maria Fanzio, MD
Medical Monitor
Novum Pharmaceutical Research Services

6/10/2016
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Director, Clinical
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2016.07.20 14:48:41 -04'00'
Date

PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol DSXS 1536 Rev 2 in accordance with FDA regulations, ICH guidelines and Good Clinical Practice. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Taro Pharmaceuticals, USA) or Novum Pharmaceutical Research Services, the company managing the study.

_____ _____

Principal Investigator Date

3.0 TABLE OF CONTENTS

4.0 SYNOPSIS

Protocol Number	DSXS 1536
Title	A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Design, Multiple-Site, Phase III Clinical Study to Evaluate the Efficacy and Safety of Desoximetasone 0.25% Shampoo in Patients with Mild to Severe Scalp Psoriasis
Objective	To evaluate the therapeutic efficacy and safety of desoximetasone 0.25% shampoo (Taro Pharmaceuticals, U.S.A., Inc.) compared to a Vehicle shampoo (Taro Pharmaceuticals, U.S.A., Inc.) in patients with mild to severe scalp psoriasis.
Sponsor	Taro Pharmaceuticals U.S.A., Inc.
Study Products	• **Test:** Desoximetasone shampoo, 0.25% (Taro Pharmaceuticals, U.S.A., Inc.) • **Vehicle:** Test Vehicle shampoo (Taro Pharmaceuticals, U.S.A., Inc.) that contains the same inactive ingredients as the Test product
Route of Administration	Topical
Treatment Randomization	1:1 (Test:Vehicle)
Patient Population	Up to 370 patients 18 years of age or older with a confirmed diagnosis of mild to severe plaque psoriasis of the scalp, will be enrolled to ensure 332 patients are available for the primary analysis.
Study Design	Randomized, double-blind, vehicle-controlled, multiple-site, parallel-design

Study Conduct	Eligible patients will be randomized in a 1:1 ratio to Test or Vehicle product. Patients will complete 3 clinic visits over a 4-week study duration as follows: Patients will administer study product once daily for 28 days starting on Day 1. The product will be left in place on the scalp for 15 minutes. During the study patients will visit the clinical center for a total of 3 scheduled visits: • Visit 1 (Day -1 to 1): Baseline/ Randomization • Visit 2 (Day 14 ± 2): Interim Visit • Visit 3 (Day 29 ± 2): End of Study or Early Termination Plaque psoriasis of the scalp will be evaluated at each visit based on dermatologic assessments including Investigator's Global Assessment (IGA) score.
Inclusion Criteria	1. Male or non-pregnant, non-lactating females 18 years of age and older. 2. If female and of child-bearing potential, have a negative urine pregnancy test at the baseline/randomization visit and prepared to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g., condom with spermicide, IUD, oral, injected, transdermal or implanted hormonal contraceptives). 3. Signed informed consent form that meets all current ICH/FDA regulations. 4. Patients with a clinical diagnosis of mild to severe plaque psoriasis of the scalp, defined by a Investigator's Global Assessment (IGA) score of at least 2 at baseline/randomization. 5. Patient is in good general health as determined by physical examination.
Exclusion Criteria	1. Patients under 18 years of age. 2. Females who are pregnant, lactating or likely to become pregnant during the study. 3. Patients whose scalp psoriasis necessitates systemic or other concomitant topical therapies during the study (concomitant treatment of body psoriasis with over the counter topical products including emollients, is allowed). 4. Patient has a scalp skin condition that would interfere with the diagnosis or assessment of plaque psoriasis of the scalp (e.g., seborrheic dermatitis, eczema, cutaneous T-cell lymphoma, or other forms of psoriasis including guttate, inverse, pustular or erythrodermic psoriasis). 5. Presence of pigmentation, extensive scarring, pigmented lesions, or sunburn in the treatment areas that could interfere with the rating of efficacy parameters, including planned extensive exposure to sunlight during the study.

	6. History of psoriasis unresponsive to topical treatments. 7. Current immunosuppression or history of organ transplant. 8. Patients who have a history of or current diagnosis of glaucoma. 9. Patients who have had surgery on the eyes or eyelids within 1 month before baseline or plan to have eye or eyelid surgery during the study. 10. Patients with active infection (including but not limited to bacterial, fungal and viral infection) and/or open wounds on the entire head and neck area. 11. Patients who have used the following on the scalp within 2 weeks before baseline: a. Topical corticosteroids b. Topical anti-psoriatic medication (e.g., salicylic acid, anthralin, coal tar, calcipotriene, tazarotene) c. Topical retinoids d. Topical anti-inflammatory agents e. Medicated shampoos for scalp psoriasis (including tar shampoos) 12. Patients who have used within 2 weeks before baseline: beta blockers, lithium preparations, anti-malarial agents or tanning booths. 13. Patients who have used topical corticosteroids on the body within 2 weeks before baseline. 14. Use within six months before baseline of biologic treatment for psoriasis (e.g., infliximab, adalimumab, alefacept). 15. Use within three months before baseline of: 1) chemotherapy or 2) radiation therapy. 16. Use within one month before baseline of: 1) systemic steroids, 2) systemic antibiotics, 3) systemic antipsoriatic treatment (e.g., methotrexate, cyclosporine, hydroxyurea), 4) PUVA therapy, 5) UVB therapy or 6) prescription strength systemic anti-inflammatory agents. 17. Use within two months before baseline of any immunosuppressive drugs (e.g., tacrolimus, pimecrolimus) or oral retinoids. 18. Changed brands/types or frequency of use of routine hair care products (shampoo, conditioner, sprays etc.) within 14 days before baseline, or intend to change during the study. 19. Receipt of any drug as part of a research study within 30 days before dosing. 20. Significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that, in the Investigator's opinion, would place the study participant at undue risk by participation. 21. Known or suspected severe renal insufficiency or severe hepatic

	disorders or severe heart disease. 22. History or current diagnosis or clinical signs and symptoms of Cushing's disease or Addison's disease or other disturbance in the HPA axis or adrenal function. 23. History of allergy or hypersensitivity to desoximetasone or history of any drug hypersensitivity or intolerance that, in the Investigator's opinion, would compromise the safety of the patient or the study. 24. Current evidence of drug abuse or history of drug abuse within 1 year before the first dose, including, in the opinion of the Investigator, history of alcohol abuse or active alcoholism. 25. Inability to understand the protocol requirements, instructions, and study-related restrictions, and the nature, scope, and possible consequences of the clinical study. 26. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions, such as uncooperative attitude, inability to return for follow-up visits, and improbability of completing the clinical study. 27. The patient is a member of the investigational study staff or a member of the family of the investigational study staff. 28. Previous participation in this study.
Efficacy Endpoint	The primary efficacy endpoint is the proportion of patients in each treatment group who are considered a Clinical Success at Day 29 ± 2, as defined by an IGA score of 0 (clear) or 1 (almost clear) with at least a 2 grades reduction from baseline at Day 29 ± 2. That is, at Day 29 ± 2, patients with an IGA score of 3 or 4 at baseline must achieve a score of 0 or 1 and patients with an IGA score of 2 at baseline must achieve a score of 0 to be considered a Clinical Success.
Therapeutic Efficacy Analysis	Superiority of the Test shampoo over the Vehicle shampoo at Day 29 ± 2 will be tested using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by clinical site, at the 5% significance level. The primary analysis will be performed using an imputation method of analysis for missing data in the Intent-to-Treat (ITT) population. Patients discontinued because of lack of treatment effect will be included in the primary analysis as treatment failures. The following two sensitivity analyses will also be performed on the primary efficacy endpoint: 1. Primary analysis will be performed also including patients without an assessment at Day 29 ± 2. Patients with missing data at Day 29 ± 2 will be considered clinical failures. 2. Primary analysis will be performed also including patients without an assessment at Day 29 ± 2. Patients from the Vehicle group with missing

	data at Day 29 ± 2 will be treated as clinical successes and patients from the Test group with missing data at Day 29 ± 2 will be treated as clinical failures.
Safety Analysis	Adverse events will be classified using standard MedDRA terminology Version 18.1 or higher and summarized by treatment group. Summary tables comparing the type, date of onset, date of resolution, incidence, severity, Investigator's opinion of relationship to the study drug, action taken, and outcome will be prepared by treatment group. If sufficient data exist, adverse event frequencies will be compared between treatments using Fisher's exact test or a similar test. Concomitant medication use during the study will be tabulated by patient. Signs and symptoms of scalp psoriasis will not be considered adverse events, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be dropped from continued participation in the study and given alternative therapy for their condition. Ocular discomfort, vital signs and skin assessments will be analyzed for both treatments. Ocular safety evaluations will be assessed at the discretion of the Investigator based on the findings of the HEENT examination performed at each visit along with the ocular discomfort symptoms reported by the patient. Ocular discomfort will be assessed by subjects and reported to staff during clinic visits (Appendix D).
Sample Size Determination	The primary statistical analysis of interest is a comparison of clinical success, as defined by an IGA score of 0 (clear) or 1 (almost clear) with at least 2 grades reduction from baseline at Day 29 ± 2, of the Test treatment, desoximetasone 0.25% shampoo, to the clinical success of the respective Vehicle shampoo in the ITT population. Based on results from Taro's Phase II study 71342608 the clinical success of the Test formulation is expected to be approximately 27% for an application duration of 15 minutes. The clinical success of the Vehicle formulation is expected to be approximately 10% for the same application duration. Based on a two-sided, Yates' continuity-corrected *Z*-test and a pooled response rate for the standard error of the difference in proportions, 166 patients in the active group and 166 patients in the placebo group of the ITT population will provide at least 97% power to demonstrate superiority at the 5% significance level ($p < 0.05$) for the active treatment over placebo. To allow for about 10% of patients who may drop out from the study or are otherwise non-evaluable, up to 370 patients may be enrolled (185 in the active group and 185 in the placebo group).

5.0 STUDY SCHEMATIC

	Visit 1	**Visit 2**	**Visit 3**
Day	**-1 to 1**	**14 ± 2**	**29 ± 2**
Procedures	Baseline/Randomization†	Interim Visit	End of Study
Informed Consent	X		
Medical History and Baseline Demographics	X		
Inclusion/Exclusion	X		
Physical Examination	X		X
HEENT Examination	X	X	X
Vital Signs	X	X	X
Pregnancy Test*	X	X	X
Percent Scalp Affected	X	X	X
Investigator's Global Assessment	X	X	X
Skin Assessment	X	X	X
Ocular Discomfort Assessment		X	X
Concomitant Medications	X	X	X
Weigh and Dispense Study Product	X	X	
Collect and Weigh Study Product		X	X
Review/Provide Patient Diary	X	X	X
Adverse Events		X	X

* Pregnancy test will be conducted for females of childbearing potential.

† Patients should administer study product once daily for 28 days starting on Day 1 through Day 28. The product will be left in place on the scalp for 15 minutes.

6.0 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Term
ADR	Adverse Drug Reaction
AE	Adverse Event
BP	Blood Pressure
C	Celsius
CRF	Case Report Form
CRO	Clinical Research Organization
eCTD	electronic Common Technical Document
FDA	Food and Drug Administration
HEENT	Head, Eyes, Ears, Nose, Throat
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
LOCF	Last Observation Carried Forward
ml	milliliter
NDA	New Drug Application
NSAID	Non-Steroidal Anti-Inflammatory Drug
OHRP	Office of Human Rights Protection
OTC	Over-the-Counter
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PSSI	Psoriasis Scalp Severity Index
PUVA	Psoralen and UltraViolet A
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
USA	United States of America

7.0 INTRODUCTION

Taro Pharmaceuticals U.S.A., Inc. (Taro) plans to submit an Investigational New Drug Application (IND) for a new formulation of desoximetasone; desoximetasone 0.25% shampoo. This product contains a potent corticosteroid to be indicated for the treatment of plaque psoriasis in patients 12 years of age or older.

7.1 Disease Being Treated

Psoriasis is an immune (T-cell)-mediated inflammatory skin disease that affects approximately 2% of the western population. The most common type of psoriasis in both adults and children is plaque psoriasis, which is characterized by the presence of raised, thickened red lesions that are covered by silvery white scales, most commonly seen on the knees and/or elbows. Although there are reports implicating a genetic association with the disease, there are also studies that have established a set of psoriasis triggers including stress, medications (such as lithium, antimalarials, indomethacin, quinidine, beta blockers), injury or infection. The condition is considered chronic although the frequency and severity of outbreak in an individual can fluctuate without apparent cause.[1-3]

At least 50% of all psoriasis cases have scalp psoriasis. Although head represents only 10% of the whole body surface, the visibility and symptoms of scalp psoriasis can be seriously debilitating for many patients, inducing social and emotional distress and negatively impacting quality of life.[4] Scalp psoriasis is more difficult to treat compared to psoriasis of the body, because the skin of the scalp is less accessible to topical treatments primarily because of the presence of hair. Moreover, vehicles used in psoriasis medications are often not cosmetically acceptable for scalp treatment, thereby negatively impacting treatment adherence. There is a need for effective, safe and cosmetically acceptable products for the treatment of scalp psoriasis to improve both compliance and response to treatment.[5]

Psoriasis severity is determined using various tools, the most extensively studied index being the Psoriasis Area and Severity Index (PASI), which is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a 0–4 scale), weighted by the % body surface area of involvement. Scalp psoriasis is often assessed using the Psoriasis Scalp Severity Index (PSSI) or the Physician's Global Assessment (PGA). However, the validity and sensitivity of such tools are not well characterized and still under investigation. Indicators for the effect of psoriasis on quality of life and response to treatment often influence the overall severity of the disease. Hence, a clinically meaningful global assessment by the physician characterizing lesions on a 5-point scale is considered most appropriate and recommended by the FDA for the purpose of psoriasis clinical trials.[7]

7.2 Availability and Efficacy of Already Approved Therapies

Treatment of plaque psoriasis depends on the severity of the condition, previous treatment regimens and personal preference of the patient. Scalp psoriasis treatments

historically include topical creams, sprays, lotions, foams, and the more recently introduced shampoos. Examples of marketed products include corticosteroids (Topicort®, Clobex™), Vitamin A and D derivatives (Tzorac®, Dovonex®), NSAIDs (salicylic acid), etc. For more severe cases, systemic therapy (methotrexate, oral retinoids, UV light, biologics, etc) may be warranted; however, the side effect profile of these products limits their use.[1,2,5,8,9]

Desoximetasone is a high potency synthetic corticosteroid marketed in a number of formulations: gel (0.05%), cream (0.05% and 0.25%), and ointment (0.05% and 0.25%). All these formulations are encompassed under the Topicort® brand, acquired by Taro Pharmaceuticals U.S.A., Inc. (Taro) in 2004. Most recently, Taro received approval on April 11, 2013 for a new dosage form (spray) under NDA #204141, Topicort® (desoximetasone) Spray, 0.25%, a super high potency formulation that is indicated for the treatment of plaque psoriasis in patients 18 years of age or older.[10] Topical application of high potency steroids at the recommended dosing levels are usually well tolerated in all populations, with less than 2% of patients reporting adverse reactions (7% in the pediatric population). The most commonly reported adverse events are burning, stinging, pruritus, and skin thinning/atrophy.[1,2,5,8,9]

Shampoos are considered a preferred treatment option for scalp psoriasis because of ease of application and cosmetic acceptability. There are many OTC coal tar shampoos in the market for treating mild scalp psoriasis. For the moderate-severe cases, a prescription shampoo containing potent corticosteroids is available in the market (Clobex™ shampoo, clobetasol propionate, 0.05%).

A new formulation of desoximetasone - Desoximetasone Shampoo, 0.25% has been developed by Taro Pharmaceuticals U.S.A., Inc. (Taro), and is the Test product used in this study.

7.3 Scientific and Statistical Considerations

This phase III study (DSXS 1536) has been designed based on review of multiple clinical studies in psoriasis, including Taro's phase II dose-ranging study on Desoximetasone Shampoo, 0.25% (DSXS 1411)[12] and those studies submitted as part of the NDA for currently marketed Taclonex® (betamethasone and calcipotriene) scalp suspension (NDA Number: 22-185)[13] and Clobex™ (clobetasol propionate) shampoo, 0.05% (Galderma Laboratories, NDA Number: 21-644).

The FDA statistical review and analyses conducted for phase III studies for Taclonex® (betamethasone and calcipotriene) scalp suspension,[13] were used to select the patient population (patients with a clinical diagnosis of mild to severe plaque psoriasis of the scalp) and the definition of Clinical Success (Investigator's Global Assessment (IGA) of disease severity score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline IGA at the end of the treatment) for this phase III study (DSXS 1536). The phase III studies for Clobex™ (clobetasol propionate) shampoo, 0.05% indicated a success

rate of 44% in the active group and approximately 2% in the vehicle group after 4 weeks of treatment.[14]

Based on these NDA studies, previous communications with Sponsor, and pre-IND discussions regarding this study with the FDA (PIND# 118881 briefing package and FDA letter dated 9/18/2013), a 28-day treatment period was considered appropriate to determine therapeutic efficacy of the Test shampoo formulation.

Taro's phase II dose-ranging study on Desoximetasone Shampoo, 0.25% (DSXS 1411) was designed to evaluate therapeutic efficacy using multiple application durations of the product. The results of this phase II study were used to determine the appropriate duration of application (15 minutes) and the expected clinical success rate for subsequent phase III efficacy studies. Based on data from this study, a population of 370 patients, with up to 185 patients receiving Test treatment and up to 185 patients receiving Vehicle treatment, for an application time of 15 minutes was considered sufficient to demonstrate efficacy, safety and superiority to Placebo for the phase III study (DSXS 1536).

The application time of 15 minutes was also supported based on results from Taro's in-vitro study that used tape stripping and vertical Franz cells to investigate the deposition of desoximetasone from a shampoo formulation.[15] At 10 minutes following application, $\geq$ 99% of the applied dose was recovered on the skin surface and no quantifiable amounts of desoximetasone were detected in the receptor compartment or inside the skin. Therefore, application durations of < 15 minutes will not be used in the Phase 3 studies. Application durations of > 15 minutes are expected to reduce the patient's dosing compliance and are thus considered impractical for patient's daily routine.

Desoximetasone is currently marketed by Taro as a gel (0.05%), cream (0.05% and 0.25%) and ointment (0.05% and 0.25%) indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, and as a spray (0.25%) indicated for the treatment of plaque psoriasis in patients 18 years of age or older. The new dosage form shampoo, the Test product for this study, was formulated with a highest marketed concentration (0.25%) to facilitate convenience by reducing contact time with the skin and to improve treatment compliance and efficacy.

7.4 Justification for use of Vehicle Shampoo

A Vehicle group will be included to confirm the sensitivity of the clinical endpoint and to demonstrate that the Test product is therapeutically superior to a Vehicle formulation that contains no active ingredient to treat scalp psoriasis. A sample size of 185 patients is the minimum number of patients that can be enrolled into the Vehicle group to ensure high statistical power (97% or more) to show a difference at $p < 0.05$ (two-sided) between the active treatment and Vehicle (according to a 1:1, Test:Vehicle randomization scheme).

7.5 Risks and Benefits

The risks and benefits to patients enrolled in clinical research studies that include a vehicle treatment group must be carefully considered based on three main criteria,

namely: the disease being treated, the availability, efficacy and safety of already approved therapies, and the scientific and statistical requirements of the desired outcome of the research study. The Office of Human Rights Protection (OHRP), a Division of the USA Federal Government's Department of Health and Human Services, has issued a detailed guidebook to Institutional Review Boards (IRBs) that includes discussion on the use of placebo in clinical studies.[17]

Patients eligible for randomized treatment will have a 50% chance of receiving the Vehicle product. Although the potential for any drug-related side effects of significance occurring during the study are low, the risk is higher in the active treatment group than in the Vehicle group.

All patients enrolled in this study will receive the benefit of free specialized medical care beyond standard medical treatment that would be expected through most health insurance plans. In addition, the patient will receive a stipend for participation to cover costs and expenses associated with trips to the medical facility.

8.0 STUDY OBJECTIVE

The objective of this study is to evaluate the therapeutic efficacy and safety of desoximetasone 0.25% shampoo (Taro Pharmaceuticals, U.S.A., Inc.) compared to a Vehicle shampoo (Taro Pharmaceuticals, U.S.A., Inc.) in patients with mild to severe scalp psoriasis.

9.0 INVESTIGATIONAL PLAN

9.1 Study Design and Plan Description

This randomized, double-blind, vehicle-controlled, parallel-group multiple-site study is designed to evaluate the therapeutic efficacy and safety of the investigational product, desoximetasone 0.25% shampoo (Taro Pharmaceuticals, U.S.A.), for the treatment of mild to severe scalp psoriasis.

Up to 370 eligible patients with scalp psoriasis that satisfy all eligibility criteria will be enrolled into the study at Visit 1. Patients must be at least 18 years of age, in overall good health. They should have a current diagnosis of mild to severe scalp psoriasis with IGA score of at least 2.

Patients who meet all inclusion/exclusion criteria will be randomized in a 1:1 ratio (Test: Vehicle) at Visit 1. At least 185 qualified patients will receive Test product and 185 patients will receive Vehicle product. The product will be left in place on the scalp for 15 minutes.

At Visit 1, patients who meet all inclusion/exclusion criteria will be randomized in a 1:1 ratio (Test: Vehicle) for 28 days of treatment:

The study products are:

- **Test**: Desoximetasone 0.25% Shampoo (Taro)
- **Vehicle**: Test Vehicle Shampoo (Taro)

Patients in each randomized treatment group will apply product once daily, according to provided instructions, for a total of 28 days starting on Day 1.

During the study patients will visit the clinical center for a total of 3 scheduled visits:

- **Visit 1 (Day -1 to 1)**: Randomization
- **Visit 2 (Day 14 ± 2):** Interim Visit
- **Visit 3 (Day 29 ± 2):** End of Study or Early Termination

The primary efficacy endpoint is the proportion of patients in each treatment group who are considered a Clinical Success, as defined by an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline IGA at Day 29 ± 2. That is, at Day 29 ± 2, patients with an IGA score of 3 or 4 at baseline must achieve a score of 0 or 1, patients with an IGA score of 2 at baseline must achieve a score of 0 to be considered a Clinical Success. The 5-point IGA score represents an overall severity of scalp psoriasis based on plaque elevation, scaling and erythema. Severity represented by a score of 0-4 is categorized as 'clear', 'minimal', 'mild', 'moderate' or 'severe'. Refer to Appendix A for IGA scoring.

The safety profile of each treatment group will be evaluated by comparing adverse events, dermal and ocular discomfort and vital signs obtained through the study duration.

Ethical consideration related to this protocol and the use of human patients will be reviewed by an IRB.

9.2 Selection of Study Design

This phase III study has been designed based on review of multiple clinical studies in psoriasis, including Taro's phase II dose-ranging study on Desoximetasone Shampoo, 0.25% (DSXS 1411)[12] and those studies submitted as a part of the NDA for currently marketed Taclonex® (betamethasone and calcipotriene) scalp suspension (NDA Number: 22-185) and Clobex® clobetasol propionate shampoo, 0.05% (NDA Number: 21-644),[13,14] and results of Taro's in-vitro study that used tape stripping and vertical Franz cells to investigate the deposition of desoximetasone from a shampoo formulation.[15] Based on these studies, previous communications with Sponsor, and pre-IND discussions with the FDA (PIND# 118881), a daily application of shampoo for 15 minutes for a 28-day treatment duration and a population of 370 patients (185 patients receiving active treatment and 185 patients receiving vehicle treatment) was considered appropriate to demonstrate therapeutic efficacy and safety of desoximetasone 0.25% shampoo (Taro) compared to a Vehicle shampoo.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Male or non-pregnant, non-lactating females 18 years of age and older.
2. If female and of child-bearing potential, have a negative urine pregnancy test at the baseline/ randomization visit and prepared to abstain from sexual

intercourse or use a reliable method of contraception during the study (e.g., condom with spermicide, IUD, oral, injected, transdermal or implanted hormonal contraceptives).

3. Signed informed consent form that meets all current ICH/FDA regulations.
4. Patients with a clinical diagnosis of mild to severe plaque psoriasis of the scalp, defined by a Investigator's Global Assessment (IGA) score of at least 2 at Screening.
5. Patient is in good general health as determined by physical examination.

9.3.2 Exclusion Criteria

1. Patients under 18 years of age.
2. Females who are pregnant, lactating or likely to become pregnant during the study.
3. Patients whose scalp psoriasis necessitates systemic or other concomitant topical therapies during the study (concomitant treatment of body psoriasis with over the counter topical products including emollients, is allowed).
4. Patient has a scalp skin condition that would interfere with the diagnosis or assessment of plaque psoriasis of the scalp (e.g., seborrheic dermatitis, eczema, cutaneous T-cell lymphoma, or other forms of psoriasis including guttate, inverse, pustular or erythrodermic psoriasis).
5. Presence of pigmentation, extensive scarring, pigmented lesions, or sunburn in the treatment areas that could interfere with the rating of efficacy parameters, including planned extensive exposure to sunlight during the study.
6. History of psoriasis unresponsive to topical treatments.
7. Current immunosuppression or history of organ transplant.
8. Patients who have a history of or current diagnosis of glaucoma.
9. Patients who have had surgery on the eyes or eyelids within 1 month before baseline or plan to have eye or eyelid surgery during the study.
10. Patients with active infection (including but not limited to bacterial, fungal and viral infection) and/or open wounds on the entire head and neck area.
11. Patients who have used the following on the scalp within 2 weeks before baseline:
    a. Topical corticosteroids
    b. Topical anti-psoriatic medication (e.g., salicylic acid, anthralin, coal tar, calcipotriene, tazarotene)

c. Topical retinoids

d. Topical anti-inflammatory agents

e. Medicated shampoos for scalp psoriasis (including tar shampoos)

12. Patients who have used within 2 weeks before baseline: beta blockers, lithium preparations, anti-malarial agents or tanning booths.
13. Patients who have used topical corticosteroids on the body within 2 weeks before baseline.
14. Use within six months before baseline of biologic treatment for psoriasis (e.g., infliximab, adalimumab, alefacept).
15. Use within three months before baseline of: 1) chemotherapy or 2) radiation therapy.
16. Use within one month before baseline of: 1) systemic steroids, 2) systemic antibiotics, 3) systemic antipsoriatic treatment (e.g., methotrexate, cyclosporine, hydroxyurea), 4) PUVA therapy, 5) UVB therapy or 6) prescription strength systemic anti-inflammatory agents.
17. Use within two months before baseline of any immunosuppressive drugs (e.g., tacrolimus, pimecrolimus) or oral retinoids.
18. Changed brands/types or frequency of use of routine hair care products (shampoo, conditioner, sprays etc.) within 14 days before baseline, or intend to change during the study.
19. Receipt of any drug as part of a research study within 30 days before dosing.
20. Significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that, in the Investigator's opinion, would place the study participant at undue risk by participation.
21. Known or suspected severe renal insufficiency or severe hepatic disorders or severe heart disease.
22. History or current diagnosis or clinical signs and symptoms of Cushing's disease or Addison's disease or other disturbance in the HPA axis or adrenal function.
23. History of allergy or hypersensitivity to desoximetasone or history of any drug hypersensitivity or intolerance that, in the Investigator's opinion, would compromise the safety of the patient or the study.
24. Current evidence of drug abuse or history of drug abuse within 1 year before the first dose, including, in the opinion of the Investigator, history of alcohol abuse or active alcoholism.

25. Inability to understand the protocol requirements, instructions, and study-related restrictions, and the nature, scope, and possible consequences of the clinical study.
26. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions, such as uncooperative attitude, inability to return for follow-up visits, and improbability of completing the clinical study.
27. The patient is a member of the investigational study staff or a member of the family of the investigational study staff.
28. Previous participation in this study.

9.3.3 Restrictions during the Study

The following medications will not be allowed for the specified wash-out periods and throughout the study.

Restricted medication	**Examples (not comprehensive)**	**Wash out**
Topical corticosteroids (on scalp or body), retinoids or anti-inflammatory agents (on scalp)	Topicort® (desoximetasone 0.25%) spray, Cortaid® (hydrocortisone 1%), Clobex® (clobetasol 0.05%), Diprolene® (betamethasone 0.05%), retinol, diclofenac, etc.	2 weeks
Topical anti-psoriatic medication (on scalp)	Psorcon® ointment/cream, Dovonex® (calcipotriene), Tazorac® (tazarotene), Vectical® (calcitriol), salicylic acid, anthralin, coal tar, etc., including medicated shampoos	2 weeks
Beta blockers, lithium preparations, anti-malarial agents or tanning booths	metoprolol, labetalol, Eskalith, Lithobid, quinine, etc.	2 weeks
Biologic treatment for psoriasis	Remicade® (infliximab), Enbrel® (etanercept), Humira® (adalimumab), etc.	6 months
Chemotherapy Radiation therapy		3 months
Systemic corticosteroids Systemic antipsoriatic treatment Systemic antibiotics PUVA therapy UVB therapy Prescription strength systemic anti-inflammatory agents	Prednisone (The use of inhaled or intranasal corticosteroids up to 1 mg/day is acceptable provided the patient has been on a stable dose for 2 weeks before dosing and will remain on the stable dose throughout the study) methotrexate, cyclosporine, hydroxyurea *aspirin for prophylactic use on a stable dose up to 325 mg per day is acceptable	4 weeks
Systemic retinoids	Soriatane® (acitretin), Isotretinoin etc	8 weeks
Systemic immunosuppressive drugs	tacrolimus, pimecrolimus	8 weeks

Concomitant treatment of body psoriasis with over the counter topical products including emollients is allowed. Prescription-strength topical and systemic anti-psoriatic treatments for body psoriasis will not be allowed during the study. In

addition, patients must have consistently used a single brand/type of hair care product (e.g., shampoo, conditioner, spray, etc.) for a minimum of 14 days prior to baseline. Patients will be asked continue using the same brand/type and frequency of use throughout the study.

9.3.4 Removal of Patients from the Study

Patients will be advised that they are free to withdraw from the study at any time for any reason, or, if necessary, the Investigator may withdraw a patient from the study to protect the health of that patient. The clinical report will include all reasons for early withdrawals.

All patients who administer at least one dose of randomized study product will be included in the safety analysis comparing the Test/ Vehicle products. Reasons for early termination may include the following:

- Worsening signs/symptoms of scalp psoriasis
- Development of an intercurrent condition or complication that could affect the safety of the patient or the validity of evaluation of the patient's clinical state to an extent considered significant by the Investigator
- Non-compliance with protocol
- Pregnancy

Patients who withdraw or are removed from the study will not be replaced.

9.3.5 Early Terminations

If a patient terminates from the study early, all efforts will be made to complete their next visit study procedures. For early termination the Investigator shall fully document the reason for early termination.

9.4 Treatments

The following treatments will be used in the study:

- **Test:** Desoximetasone shampoo, 0.25% (Taro Pharmaceuticals, U.S.A., Inc.), applied once daily for 28 days
- **Vehicle:** Test Vehicle shampoo (Taro Pharmaceuticals, U.S.A., Inc.), applied once daily for 28 days

9.4.1 Treatments Administration

Patients will be provided with verbal and written instructions on how to administer study product. The study product is to be applied to psoriasis-affected areas of the dry scalp once a day. Patients are to move the hair away from the dry scalp so that one of the affected areas is exposed. A small amount of the study shampoo is to be applied directly to the affected area by gently squeezing the

bottle. The shampoo is to be gently rubbed into the affected area. The same procedure is to be followed for other affected areas on the scalp. Patients will be instructed to use only enough to cover affected areas and avoid application to face, groin, armpits, lips or eyes. If during application the product comes in contact with the eyes or eyelids, patients will be instructed to rinse the area with abundant water immediately. Patients should not cover the head with a shower cap while the shampoo is on the scalp. The shampoo is to be left in place for 15 minutes before adding water, lathering and rinsing hair and scalp completely.

Patients will be instructed to begin dosing on the evening of enrollment or in the morning on the day following enrollment. Treatments are to be applied once daily at approximately the same time, on each day, for 28 days starting on Day 1.

Patients should not apply more than 50 ml of study product per week.

9.4.2 Identity of Investigational Product

The following products will be used in the study:

- **Test:** Desoximetasone 0.25% shampoo, manufactured by Taro Pharmaceuticals.
- **Placebo:** Test Vehicle shampoo, manufactured by Taro Pharmaceuticals.

Study products will be supplied in 120 ml bottles.

All randomized study products will be blinded and packaged in blinded sealed boxes. Each bottle will be identified by a label bearing the Sponsor name, protocol number, randomization number, treatment duration, a statement that the study product is for Investigational Use Only, a place for patient initials and the date the bottle was dispensed. The study staff will dispense the study product bottle only to those patients identified by the Investigator. The study staff will instruct the patients on the use and return of study product.

Individual bottles of study product will be packaged in blocks. The randomization will be generated in blocks of 4. Four (4) patients' worth of product (2 patients worth of Test product, 2 patients worth of Vehicle product), based on a 1:1 randomization ratio, will be packed into a larger box. This larger box will be designated "one block" of study product. Further details for randomization are provided in section 9.4.3.

The study product will be shipped to each Investigator's site from a centralized pharmacy. The Principal Investigator at each site is responsible for ensuring that all study products are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study product will be maintained in accordance with federal regulations. Study product will be stored at controlled room temperature 15-30°C (59-86°F).

Once the site has been notified that they may do so, all unused study product and empty or partially used bottles of study product may be returned to the Sponsor or designee.

9.4.3 Method of Assigning Patients to Treatment Groups

At Visit 1 eligible patients will be randomized to the study and assigned a randomization number. Patient numbers will consist of a 2-digit site number and 4-digit randomization number. The 4-digit randomization numbers will be assigned in ascending order beginning with the lowest number at each study site.

The study product will be packaged and blinded by an independent clinical packaging company. The randomization will be generated in blocks of 4 to accommodate the 1:1 randomization scheme (2 Test:2 Vehicle).

Each eligible patient will receive 2 x 120 ml bottles of study product (Test or Vehicle). Patients will be randomized to a treatment group in a blinded fashion by assigning randomization numbers in ascending sequential order starting with the lowest available randomization number at each site. All patients randomized will be identified by initials, date of birth, and a unique six-digit patient number. A perforated two-part label will be attached to each of the small sized boxes of study product supplies. Both pieces of the label will include the following information: Protocol number, randomization number, dosing instructions, space for patient's initials, statement that the study product is for investigational use only, space for dispensing date and the Sponsor's name. One part of the label shall remain attached to the box. The other part will be removed prior to dispensing and attached to the patient source documents. In addition all patients will be provided with written instructions on how to use the study product. Prior to dispensing, study product will be weighed.

9.4.4 Study Blind

The Investigator, staff at the study site and study monitors will be blinded to the patient assignment. Each study site will have at least one Independent Dispenser. The role of the Independent Dispenser is to dispense and collect all study product bottles from the patients and to ensure the study product logs are reported correctly. They should not be involved in collecting any efficacy or safety data in the study, thus ensuring the integrity of the study blind.

To ensure that information that could potentially bias handling of data is not disclosed, the clinical packaging company will hold the randomization scheme until release is requested by the Sponsor or designee. Unblinding code in the form of a scratch off portion of the product label attached to the source documents will be retained at the study site to be opened in case of medical emergency only.

Whenever possible, the Novum Medical Monitor must be contacted before breaking the blind for any patient. In the event the blind is broken for any reason Sponsor and Novum will be notified as soon as possible in writing of the details of the occurrence.

The bottles used for both study products will be similar in size, shape and color. This will allow the treatment phase of the study to be conducted under double-blind conditions, such that neither the patient nor the Investigator or study staff members will know the identity of each patient's treatment.

9.4.5 Compliance

Patients will be considered compliant with dosing if they administered 75%-125% of the required 28 doses and did not miss 4 or more consecutive doses and did not dose more than twice on any particular day. Compliance with dosing will be verified by the use of patient diaries.

9.5 Study Conduct

9.5.1 Visit 1 (Day -1 to 1) Baseline/Randomization [First day of application is Day 1]

1. **Informed Consent**: Patients who are willing to comply with study procedures will read and sign the informed consent form.
2. **Medical History and Baseline Demographics**: Patient's demographic and medical history including use of medications within the last 24 weeks will be reviewed.
3. **Inclusion/Exclusion Criteria**: Patients will be screened for eligibility based on inclusion/exclusion criteria.
4. **Physical Examination**: An overall assessment of health status will be conducted at the clinic.
5. **HEENT Examination**: A general exam of the head, eyes, ears, nose and throat will be conducted at the clinic.
6. **Vital Signs**: Pulse, blood pressure (BP), temperature and respiratory rate (RR) will be recorded.
7. **Pregnancy Test**: A urine pregnancy test will be required of all female patients of childbearing potential before enrollment.
8. **Percent Scalp Affected**: Patient's scalp will be examined by Investigator/designated clinician to determine the percent surface area affected with plaque psoriasis. Refer to Appendix C.
9. **Investigator's Global Assessment (IGA)**: Patient's scalp will be examined to determine a psoriasis severity score based on a global assessment of plaques by the Investigator/designated clinician (refer to Appendix A). Patients with a score of 2 or more, indicating mild-severe psoriasis will be included in the study.

10. **Skin Assessment**: Skin irritation symptoms will be evaluated by an Investigator as a part of baseline safety assessments and a score will be documented (refer to Appendix B).
11. **Weigh/Dispense Study Product**: Study product bottle will be weighed and dispensed with dosing instructions.
12. **Review/Provide Diary**: A dosing diary with instructions will be provided.
13. Schedule Visit 2.

9.5.3 Visit 2 (Day 14 ± 2): Interim Visit

1. **HEENT Examination**: A general exam of the head, eyes, ears, nose and throat will be conducted at the clinic.
2. **Vital Signs**: Pulse, blood pressure (BP), temperature and respiratory rate (RR) will be recorded.
3. **Pregnancy Test**: For women of childbearing potential, a urine pregnancy test will be performed to evaluate pregnancy.
4. **Percent Scalp Affected**: Patient's scalp will be examined by Investigator/designated clinician to determine the percent surface area affected with plaque psoriasis. Refer to Appendix C.
5. **Investigator's Global Assessment (IGA)**: Patient's scalp will be examined to determine the psoriasis severity score based on a global assessment of plaques by the Investigator/designated clinician (refer to Appendix A).
6. **Skin and Ocular Assessments**: Skin irritation symptoms will be evaluated by an Investigator and a score will be documented. Patients will also be questioned about any ocular discomfort as a part of safety assessments (refer to Appendices B and D).
7. **Collect/Weigh/Dispense Study Product:** Study product bottle will be collected and weighed. A new bottle will be weighed and dispensed along with dosing instructions.
8. **Review/Provide Diary**: Patient diary will be reviewed for dosing compliance. A new dosing diary with instructions will be provided.
9. **Concomitant Medications**: Patients will be questioned about any new medications taken since last visit.
10. **Adverse Events**: Patients will be questioned about any health status changes/adverse events since last visit. All events will be recorded.
11. Schedule Visit 3.

9.5.4 Visit 3 (Day 29 ± 2): End of Study or Early Termination

1. **Physical Examination**: An overall assessment of health status will be conducted at the clinic.
2. **HEENT Examination**: A general exam of the head, eyes, ears, nose and throat will be conducted at the clinic.
3. **Vital Signs**: Pulse, BP, temperature and RR will be recorded.
4. **Pregnancy Test**: For women of childbearing potential, a urine pregnancy test will be performed to evaluate pregnancy.
5. **Percent Scalp Affected**: Patient's scalp will be examined by Investigator/designated clinician to determine the percent surface area affected with plaque psoriasis. (Refer to Appendix C).
6. **Investigator's Global Assessment (IGA)**: Patient's scalp will be examined to determine the psoriasis severity score based on a global assessment of plaques by the Investigator/designated clinician (refer to Appendix A).
7. **Skin and Ocular Assessments**: Skin irritation symptoms will be evaluated by an Investigator and a score will be documented. Patients will also be questioned about any ocular discomfort as a part of safety assessments (refer to Appendices B and D).
8. **Collect/Weigh Study Product**: Study product bottle will be collected and weighed.
9. **Review Diary**: Patient diary will be reviewed for dosing compliance.
10. **Concomitant Medications**: Patients will be questioned about any new medications taken since last visit.
11. **Adverse Events**: Patients will be questioned about any health status changes/adverse events since last visit. All events will be recorded.

9.6 Study Procedures

9.6.1 Informed Consent

At Visit 1, before any study related procedures, the study patient must sign the IRB-approved consent form. The consent form will be reviewed and approved by an Institutional Review Board before study commencement. No patient will be entered into the study without reading, understanding and signing an informed consent. For illiterate patients, verbal consent should be obtained in the presence of and be countersigned by a literate witness. If any other language is required, translation will be performed by a certified translator. A copy of the ICF will be provided to the patient.

9.6.2 Demographics

At Visit 1, each patient shall be required to provide basic demographic information: date of birth, gender, ethnicity and race.

9.6.3 Medical History

At Visit 1, patients will be questioned about personal medical history, including acute and chronic medical history and medical history relevant to their scalp psoriasis, as well as all medication use within the past 24 weeks.

9.6.4 Vital Signs

The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate) at each clinic visit.

9.6.5 Physical Examination and HEENT Examination

An overall assessment of health status will be conducted at Visits 1 and 3. A head, eye, ear, nose, throat (HEENT) examinations will be conducted at each clinic visit.

Ocular safety evaluations will be assessed at the discretion of the Investigator based on the findings of the HEENT examination performed at each visit along with the ocular discomfort reported by the patient. Medical records associated with the ocular safety evaluation should be obtained for the study chart.

9.6.6 Concomitant Medication Use

At each clinic visit, patients will be questioned about current and concomitant medication use. Patients will also be questioned about ongoing or new concomitant medication use during the treatment period at Visits 2 and 3.

9.6.7 Pregnancy Test

All females of childbearing potential will have a urine pregnancy test performed at each specified clinic visit. The test must be negative at Visit 1 for the patient to be eligible for inclusion in the study. If the patient is of non-childbearing potential, then the source document must list the reason why she is of non-childbearing potential (e.g., premenarchal).

Any patient who becomes pregnant during the study must be discontinued and end of study procedures (Visit 3) completed. The outcome of the pregnancy should be followed by the Investigator to the conclusion of the pregnancy.

9.6.8 Dispensing Study Product

An Independent Dispenser will weigh and dispense randomized study product bottle at Visits 1 and 2, with instructions on dosing. Patients will be instructed to begin dosing on the evening of enrollment or in the morning on the day following enrollment. The Independent Dispenser will ensure the study product logs are

reported correctly. They should not be involved in collecting any efficacy or safety data in the study, thus ensuring the integrity of the study blind.

9.6.9 Collecting Study Product

Study product bottles will be collected at Visits 2 and 3 and weighed.

9.6.10 Dosing Instructions and Diary

Patients will be given a dosing diary at Visits 1 and 2 along with instructions on how to complete the diary. Patients will be asked to record the time and date of each dose, AEs, and concomitant medications throughout the study. The diary will be collected and reviewed at each subsequent visit by the study staff.

9.6.11 Dosing Compliance

Dosing compliance will be checked by site staff at Visits 2 and 3 by reviewing patient diary entries. Patients will be considered compliant with dosing if they administered 75%-125% of the required 28 doses and did not miss 4 or more consecutive doses and did not dose more than twice on any particular day.

9.6.12 Percent Scalp Affected

Patient's scalp will be examined by Investigator/ designated clinician to determine the percent surface area affected with plaque psoriasis at all visits. At each subsequent visit, the % affected area will be monitored and documented. Refer to Appendix C.[18]

9.6.13 Investigator's Global Assessment (IGA)

Patient's scalp will be examined to determine the psoriasis severity score based on a global assessment of plaques by the Investigator/designated clinician (refer to Appendix A).

9.6.14 Skin Safety Assessments

As a part of safety evaluation at each clinic visit, the Investigator/designated clinician will conduct an careful assessment of the scalp and adjacent skin (e.g., ears, forehead and neck) for local tolerability and a score will be documented (refer to Appendix B).

9.6.15 Ocular Discomfort Assessment

Ocular discomfort will be assessed by subjects and reported to clinic staff during scheduled visits (refer to Appendix D). If the shampoo comes into contact with the patient's eyes, the patient will be asked to report the contact at each visit.

Ocular safety evaluations will be assessed at the discretion of the Investigator based on the findings of the HEENT exam performed at each visit along with the ocular discomfort reported by the patient. Medical records associated with the ocular safety evaluation should be obtained for the study chart.

9.7 Adverse Events

The patients will be monitored throughout the study for any Adverse Events. AEs will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the MedDRA (Version 18.1 or higher) Adverse Event Dictionary. The patients will be encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each AE will be determined by the staff based on observation and questioning of the patients. The Investigator will judge the relationship of the event to the study treatments. Adverse events should be followed up until they have resolved or stabilized. In the opinion of the Investigator, if the patient suffers an AE that warrants discontinuation of the study drug due to interference with age-appropriate instrumental ADL (Activities of Daily Living), for example preparing for meal, shopping for groceries or clothing, using the telephone, etc. the patient will be followed until the AE resolves or is considered stable. Any subject that discontinues the study because of an adverse event will be followed until resolution or stabilization of the adverse event.

9.7.1 Adverse Event Definitions

Adverse Event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease, temporally associated with the use of a medicinal (investigational) product, whether or not related to this product. This includes events not seen at baseline, or worsened even if present at baseline.

Unexpected Adverse Event: An adverse event where the nature or severity of is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Adverse Drug Reaction: All noxious and unintended responses to a medical product related to any dose should be considered adverse drug reactions. The response to a 'medical product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

9.7.2 Severity of Adverse Event

The severity of the adverse event will be graded by the Investigator using the following criteria as guidelines:

- MILD: Awareness of symptom but does not interfere with routine activities.
- MODERATE: Discomfort sufficient to interfere with routine activities.
- SEVERE: Impossible to perform routine activities.

9.7.3 Relationship of Adverse Event

Relationship to the Study Product

- NOT RELATED: Any AE that is clearly not related to use of the study drug.
- POSSIBLE: The association of the AE with the study drug is unknown; however, a relationship between the drug and event cannot be ruled out.
- PROBABLE: There is reasonable temporal relationship between the use of the study drug and the AE. Based upon the Investigator's clinical experience, the association of the event with the study drug seems likely.
- DEFINITE: The AE occurs following the application of the study drug and it cannot be reasonably explained by any other known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of treatment administered to the patient. It disappears or decreases upon discontinuation of the study product and reappears on a re-challenge of the study drug.

9.7.4 Patient's Participation Stopping Criteria

In the opinion of the Investigator, if the patient suffers an AE that warrants discontinuation of the study drug because of interference with age-appropriate instrumental ADL (Activities of Daily Living), for example preparing for meal, shopping for groceries or clothing, using the telephone, etc. the patient will be followed until the AE resolves or is considered stable. Any subject that discontinues the study because of an adverse event will be followed until resolution or stabilization of the adverse event.

9.8 Serious Adverse Events

9.8.1 Definition of a Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose suggests a medically significant hazard, including any event that:

- Results in death – includes all deaths, even those that appear to be completely unrelated to study treatment (e.g., car accident where patient is a passenger).
- Is life–threatening – in the view of the Investigator, the patient is at immediate risk of death at the time of the event.
- Results in persistent or significant disability or incapacity (substantial disruption of one`s ability to conduct normal life).
- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Causes congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the serious outcomes listed above (e.g., intensive treatment in an emergency room, convulsions that do not result in hospitalizations). Emergency Room visits that require medical or surgical intervention to prevent one of the other serious outcomes listed above are considered a Serious Adverse Event.

9.8.2 Reporting Serious Adverse Events

Investigator Reporting of SAEs

Adverse events which are evaluated by the Investigator as "Serious" will be reported to the Sponsor and IRB within 24 hours of notice whether or not they are considered expected or drug-related. All SAEs will be reported as per applicable regulations. All SAEs encountered during the study will be reported on the appropriate form and summarized in the final report.

Any serious or unexpected adverse events should be reported to Novum within 24 hours. Following is the contact information:

Gail Gongas
Vice President, Clinical Trials
Cell Phone 412-606-1603
Phone 412-363-3300 x 522
Fax 412-291-3171

Or

Paolo Maria Fanzio, MD
Medical Monitor
Pittsburgh, PA 15206
Phone: 412-363-3300 x597
Fax: 412-924-0522

Novum will report any Serious Adverse Event to Taro.

Documentation should be sent to Taro's Study Manager and/or Taro's Drug Safety Department listed below:

Taro Operation Coordinator, Clinical:
Danielle Simpson
Operation Coordinator, Clinical
Phone: (914) 345-9001 x6234
Email: Danielle.Simpson@Taro.com

Taro Drug Safety Manager:
Margo Lacy Wyatt, RN, BSN,
Drug Safety Manager, Medical Affairs

Phone: 914-345-9001 Ext. 6758
Email: Margo.Wyatt@taro.com
and TAROPVUS@TARO.com

Investigators will be informed of any SAEs reported at other study sites within 15 days from the initial report.

10.0 STATISTICAL METHODS

10.1 Statistical Plan

A Statistical Analysis Plan (SAP), detailing the intended statistical analysis of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused and spurious data will be included in the Statistical Analysis Plan.

All statistical analysis will be conducted using SAS®, Version 9.4 or higher.

10.2 Determination of Sample Size

The primary statistical analysis of interest is a comparison of clinical success, as defined by an IGA score of 0 (clear) or 1 (almost clear) with at least 2 grades reduction from baseline at Day 29 ± 2, of the Test treatment, desoximetasone 0.25% shampoo, to the clinical success of the respective Vehicle shampoo in the ITT population. Based on results from Taro's Phase II study 71515008, the clinical success of the Test formulation is expected to be approximately 27% for an application duration of 15 minutes. The clinical success of the Vehicle formulation is expected to be approximately 10% for the same application duration. Based on a two-sided, Yates' continuity-corrected *Z*-test and a pooled response rate for the standard error of the difference in proportions, 166 patients in the active group and 166 patients in the placebo group of the ITT population will provide at least 97% power to demonstrate superiority at the 5% significance level ($p < 0.05$) for the active treatment over placebo. To allow for about 10% of patients who may drop out from the study or are otherwise non-evaluable, up to 370 patients may be enrolled (185 in the active group and 185 in the placebo group).

10.3 Study Populations

10.3.1 Intent-to-Treat (ITT) Population

The ITT population will include:

- All randomized subjects.

10.3.2 Safety Population

- All patients who were randomized and applied at least one dose of the study product.

10.4 Baseline Comparability

Baseline comparability of each treatment group will be evaluated separately in the ITT and Safety populations. Comparative analyses will use appropriate statistical tests (e.g., one-way analysis of variance, Cochran-Mantel-Haenszel test).

The following baseline demographics (determined from their initial study visit) will be evaluated:

- Age (years)
- Gender (male/female)
- Ethnicity (Hispanic/non Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)
- % Scalp affected
- Number of months and/or years patient has suffered from symptoms caused by scalp psoriasis

Descriptive statistics by treatment group will be presented.

10.5 Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients in each treatment group who are considered a Clinical Success at Day 29 ± 2, as defined by an IGA score of 0 (clear) or 1 (almost clear) with at least a 2 grades reduction from baseline at Day 29 ± 2. That is, at Day 29 ± 2, patients with an IGA score of 3 or 4 at baseline must achieve a score of 0 or 1 and patients with an IGA score of 2 at baseline must achieve a score of 0 to be considered a Clinical Success.

10.6 Efficacy Analysis

10.6.1 Primary Analysis

Superiority of the Test shampoo over the Vehicle shampoo at Day 29 ± 2 will be tested using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by clinical site, at the 5% significance level. The primary analysis will be performed using an imputation method of analysis for missing data in the Intent-to-Treat (ITT) population. Details of the imputation method will be delineated in the SAP. Patients discontinued because of lack of treatment effect will be included in the primary analysis as treatment failures.

10.6.2 Sensitivity Analyses

The following two sensitivity analyses will also be performed on the primary efficacy endpoint:

1. Primary analysis will be performed also including patients without an assessment at Day 29 ± 2. Patients with missing data at Day 29 ± 2 will be considered clinical failures.
2. Primary analysis will be performed also including patients without an assessment at Day 29 ± 2. Patients from the Vehicle group with missing data at Day 29 ± 2 will be treated as clinical successes and patients from the Test group with missing data at Day 29 ± 2 will be treated as clinical failures.

10.7 Safety Analysis

Adverse events will be classified using standard MedDRA terminology Version 18.1 or higher and summarized by treatment group. Summary tables comparing the type, date of onset, date of resolution, incidence, severity, Investigator's opinion of relationship to the study drug, action taken, and outcome will be prepared by treatment group. If sufficient data exist, adverse event frequencies will be compared between treatments using Fisher's exact test or a similar test.

Concomitant medication use during the study will be tabulated by patient.

Signs and symptoms of scalp psoriasis will not be considered adverse events, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be dropped from continued participation in the study and given alternative therapy for their condition.

Ocular discomfort, vital signs and skin assessments will be analyzed for both treatments. Ocular safety evaluations will be assessed at the discretion of the Investigator based on the findings of the HEENT examination performed at each visit along with the ocular discomfort symptoms reported by the patient. Ocular discomfort will be assessed by subjects and reported to staff during clinic visits (Appendix D).

11.0 REGULATORY OBLIGATIONS

11.1 Institutional Review Board

The study protocol, informed consent form, Investigator's Brochure, or package insert (as applicable), and any specific advertising will be submitted to, and approved by, an Institutional Review Board (IRB) before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification of the board's approval along with a description by profession and gender of the board's composition will be provided to the Sponsor.

11.2 Study Documentation

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs) and all applicable regulations, including the Federal Food, Drug and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320, and any IRB requirements relative to clinical studies; and the Declaration of Helsinki, June 1964,

as modified by the 64th World Medical Association General Assembly, October 2008. The Investigator will permit trial-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data/documents.

11.2.1 Protocol

The Investigator indicated on FDA Form 1572 will act as the Principal Investigator at each study site. Protocols will be noted as approved by placement of the Novum Representative's signature on the cover page. The Sponsor of the study will also approve the protocol by having a study-responsible individual sign the protocol cover page.

11.2.2 Informed Consent

An Informed Consent Form (ICF) that includes all of the relevant elements currently required by FDA and local State regulations will be provided to each prospective study patient before enrollment into the study. The type and method of study, tests to be administered, any potential or possible hazards, and the patient's right to withdraw from the study at any time will be explained to the patients by the Investigator or designee. Once the Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the patient will be asked to give consent by signing and dating in the appropriate areas of the ICF. The Investigator or designee will also sign and date the form, along with a staff member who will sign the ICF as a witness to verify that the patient has indeed received information. For illiterate patients, verbal consent should be obtained in the presence of and be countersigned by a literate witness. If any other language is required, translation will be performed by a certified translator. A copy of the ICF will be provided to the patient.

11.2.3 Protocol and Informed Consent Changes

Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version and approved by the IRB. Any revision that substantially alters the study design or increases potential risk to the patient requires the patient's consent to continue in the study. Revisions to the original ICF will also be approved by the IRB. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor.

11.2.4 Source Documents and Case Report Forms

All patients will be identified by initials, date of birth, and a unique patient number. Source documents will be used to record all study-related data. Source document entries will be used to complete Case Report Forms (CRFs). All data and CRFs will be reviewed, evaluated and signed by the Investigator, as required.

11.2.5 Drug Accountability

All study product receipt, inventory, dispensing, dosing and reconciliation records will be maintained in compliance with Federal Regulations. The study product will be dispensed to qualified study patients according to established procedures. At the end of the study (after the database has been locked) all used and unused study product will be returned to Sponsor or designee.

11.2.6 Drug Storage

All study product will be stored at controlled room temperature 15-30°C (59-86°F), in a secure place with access by authorized individuals only. The Investigator will be responsible for maintaining accurate records of study product receipt, dispensing, and return. At the end of the study, all partially used and unused study product will be returned to Sponsor or designee.

11.2.7 Pregnancies

Patients with a positive pregnancy test at Visit 1 will not be enrolled in the study. Patients who report that they have become pregnant during the study or have a positive pregnancy test at any clinic visit will be followed to completion of the pregnancy. The pregnancy will be reported as an AE.

Female patients of childbearing potential must have been using and must agree to continue to use accepted methods of birth control, throughout the study. All female patients are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized or have been postmenopausal for at least 1 year. Abstinence is an accepted method of birth control. Alternatively, any of the following methods of birth control are acceptable: oral contraceptives, contraceptive patches/implants (e.g., Skyla® and Mirena®), Depo-Provera®, double barrier methods (e.g., condom and spermicide) or IUD. Before study enrollment women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation.

A negative result of a urine pregnancy test having a minimum sensitivity of at least 25 mIU/ml for hCG should be obtained, before study participation. Pregnancy testing will be performed at each specified clinic visit and the results of all pregnancy tests (positive or negative) will be documented.

If following initiation of study treatment, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of study product exposure, the study product will be permanently discontinued. The Principal Investigator must immediately notify the Medical Monitor of this event. Reporting timelines and Novum/Sponsor contact will be consistent with SAE reporting guidelines (see section 9.8.2 of the protocol), i.e., pregnancies will be reported to the Sponsor/Novum within 24 hours.

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient. Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Principal Investigator must report to the sponsor follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks after birth.

11.2.8 Reporting Safety Information to the IRB

The Investigator must promptly report to the Investigator's IRB all unanticipated problems involving risks to patients. This includes death from any cause and all serious adverse events occurring during the study, regardless of the assessed causality.[23]

11.2.9 Record Retention

All drug accountability records, CRFs, source data and related regulatory documents must be retained for at least ten years following completion of the study or for two years after the test product has been approved for marketing by the Food and Drug Administration.

11.2.10 Study Monitoring and Auditing

Novum will be responsible for monitoring the study according to Good Clinical Practice and applicable regulations. Monitoring visits are for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The clinical site will make all records associated with the study available to Novum's representative during such visits and audits

The study may be subject to audit by the Sponsor, Sponsor Representative or by regulatory authorities. If such an audit occurs the Investigator must agree to allow access to required patient records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of study procedures.

11.2.11 End of the Trial

The end of the trial is defined as the time at which the last patient has completed their last visit in the study. Upon completion of the study, the study drug will no longer be available to the patient but the Investigator can, at their discretion, discuss alternative treatments with the patient.

11.2.12 Clinical Study Report

At the end of the study a full report per requirements of Sponsor and regulatory authorities will be prepared which will include a narrative of the clinical conduct and results of the study, a statistical report including a description of the analysis performed, and other documentation as may be appropriate. The report will be in

electronic format according to eCTD and ICH formatting standards and guidelines. ANDA summary tables will also be generated. Data sets will be provided in SAS® transport (.xpt) format with appropriate description (Read Me) files as required by FDA.

12.0 REFERENCES

1 www.psoriasis.org.
2 National Clinical Guideline Centre, U. Assessment and management of psoriasis. *NCGC Guideline* (2012).
3 Jacob, S. Corticosteroid and Fragrance Allergy Exacerbating Scalp Psoriasis. *J Clin Aesthet Dermatol* **7**, 54-55 (2014).
4 Bucolo, S. Head and Neck Psoriasis. *Psoriasis, Dr. Jennifer Soung (Ed.), ISBN: 978-953-307-878-6, IntechOpen* (2012).
5 Luger, T. A. *et al.* A study of the safety and efficacy of calcipotriol and betamethasone dipropionate scalp formulation in the long-term management of scalp psoriasis. *Dermatology* **217**, 321-328, doi:10.1159/000155642 (2008).
6 Feldman, S. R. & Krueger, G. G. Psoriasis assessment tools in clinical trials. *Annals of the rheumatic diseases* **64 Suppl 2**, ii65-68; discussion ii69-73, doi:10.1136/ard.2004.031237 (2005).
7 Louden, B. A., Pearce, D. J., Lang, W. & Feldman, S. R. A Simplified Psoriasis Area Severity Index (SPASI) for rating psoriasis severity in clinic patients. *Dermatology online journal* **10**, 7 (2004).
8 Augustin, M. *et al.* Topical long-term therapy of psoriasis with vitamin D(3) analogues, corticosteroids and their two compound formulations: position paper on evidence and use in daily practice. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG* **12**, 667-682, doi:10.1111/ddg.12396 (2014).
9 Samarasekera, E. J., Sawyer, L., Wonderling, D., Tucker, R. & Smith, C. H. Topical therapies for the treatment of plaque psoriasis: systematic review and network meta-analyses. *Br J Dermatol* **168**, 954-967, doi:10.1111/bjd.12276 (2013).
10 Taro Pharmaceuticals. Package Insert for TOPICORT® (desoximetasone) Topical Spray, 0.25%. (2013).
11 Galderma. Package Insert for Clobex 0.05% shampoo. (2011).
12 Taro's phase II dose-ranging study on Desoximetasone Shampoo, 0.25% (DSXS 1411).
13 FDA. Statistical REVIEW AND EVALUATION for NDA22-185 (Taclonex® (betamethasone and calcipotriene) scalp suspension).
14 FDA. Summary Basis of Approval, NDA 21-644, Clobex shampoo, 0.05%. (2004).
15 Taro in-vitro study investigated the deposition of Desoximetasone from shampoo formulation using vertical Franz cells.
16 ICH. Choice of Control Group and Related Issues in Clinical Trials E10. **20 July** (2000).
17 Penslar. IRB Guidebook, Office for Human Rights Protection. *US Department of Health and Human Services* (1993).
18 Olsen, E. A. *et al.* Alopecia areata investigational assessment guidelines--Part II. National Alopecia Areata Foundation. *Journal of the American Academy of Dermatology* **51**, 440-447, doi:10.1016/j.jaad.2003.09.032 (2004).
19 FDA. 21CFR 320 Procedures for Determining the Bioavailability or Bioequivalence of Drug Products. *Department of Health and Human Services, Subchapter D-Drugs for Human Use* **5** (2014).
20 FDA. 21CFR Part 50 Protection of Human Subjects. *Department of Health and Human Services, Subchapter A-General* **1** (2014).
21 FDA. 21CFR Part 56 Institutional Review Boards. *Department of Health and Human Services, Subchapter A-General* **1** (2014).
22 World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama* **310**, 2191-2194, doi:10.1001/jama.2013.281053 (2013).
23 FDA. 21CFR 312.32: IND Safety Reporting. (2010).

24 ICH. Structure and Content of Clinical Study Reports E3. Step 4 version. (1996).

13.0 APPENDICES

13.1 APPENDIX A

Investigator's Global Assessment (IGA) of Disease Severity of Scalp Psoriasis

Score	Category	Description
0	Clear	Plaque elevation: no evidence of plaque elevation above normal skin level. Scaling: no evidence of scaling Erythema: no redness
1	Minimal	Plaque elevation: very slight elevation above normal skin level, easier felt than seen Scaling: limited amount of very fine scales partially covers some of the plaques Erythema: very few of the plaques are light red
2	Mild	Plaque elevation: slight but definite elevation above the normal skin level, typically with edges that are indistinct or sloped on some of the plaques. Scaling: mainly fine scales, some plaques are partially covered. Erythema: some plaques are light red
3	Moderate	Plaque elevation: moderate elevation with rounded or sloped edges on most of the plaques Scaling: somewhat coarser scales; most plaques are partially covered. Erythema: most plaques are red
4	Severe	Plaque elevation: marked to very marked elevation, with hard to very hard sharp edges on virtually all or all of the plaques. Scaling: coarse, thick scales; virtually all or all plaques are covered; rough surface. Erythema: virtually all or all plaques are bright to dusky red.

13.2 APPENDIX B

Skin Assessment (Forehead, Neck and Ears)

At each clinic visit, the Investigator will evaluate the scalp and the adjacent skin (head, neck and ears) for irritation using the following scale:

Dermal Response and Other Effects Scoring

Dermal Response

0 = no evidence of irritation

1 = minimal erythema, barely perceptible

2 = definite erythema, readily visible; minimal edema or minimal papular response

3 = erythema and papules

4 = definite edema

5 = erythema, edema, and papules

6 = vesicular eruption

7 = strong reaction spreading beyond the application site

Other Effects

N = No other observations (numerical score = 0)

A = Slightly glazed appearance (numerical score = 0)

B = Marked glazed appearance (numerical score = 1)

C = Glazing with peeling and cracking (numerical score = 2)

F = Glazing with fissures (numerical score = 3)

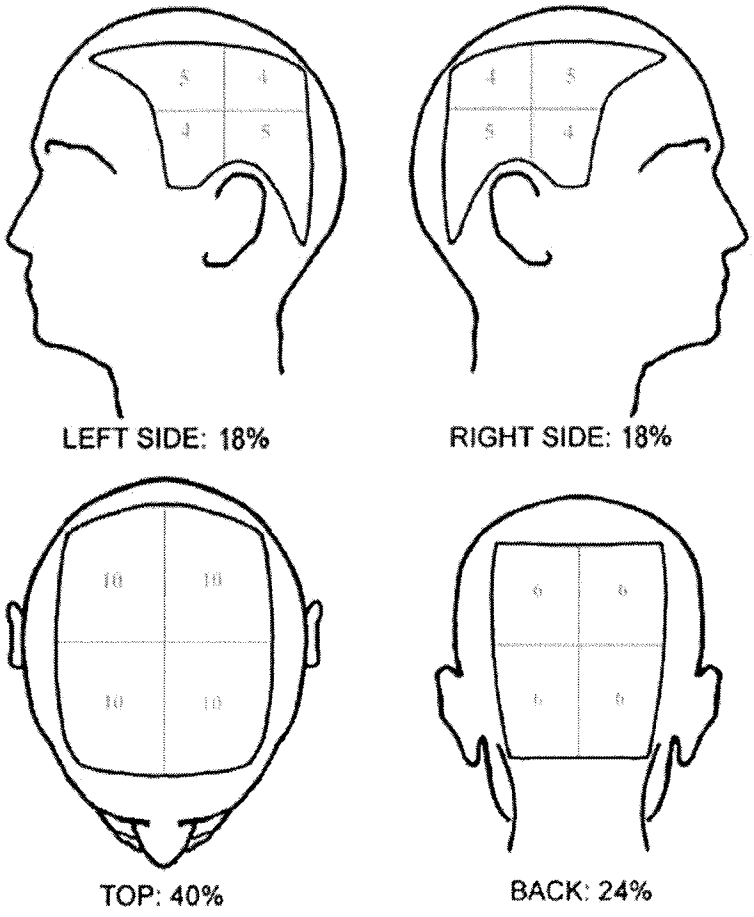
G = Film of dried serous exudates covering all or part of the application site (numerical score = 3)

H = Small petechial erosions and/or scabs (numerical score = 3)

13.3 APPENDIX C

Percent Scalp Affected- [18]

Investigators will use the following chart to identify areas and estimate scalp surface area affected by psoriasis plaques.



13.4 APPENDIX D

Ocular Discomfort Assessment

At Visits 2 and 3 the patient will be asked to assess if any ocular discomfort was experienced, YES or NO, since the last clinic visit.

If YES is reported, the patient will be asked to report the signs and symptoms that apply from the list below or indicate any OTHER signs and symptoms experienced:

Redness	Stinging
Itching	Blur (decrease in vision)
Pain	Increased sensitivity
Swelling	Watery eyes
Burning	Spots, flashes and floaters
Eye Discharge	Foreign body sensation

In addition, the patient will be asked to indicate if the shampoo came into contact with their eye, YES or NO, since the last clinic visit. If YES is reported, the patient will be asked to rate the discomfort at the time of contact as None, Mild, Moderate or Severe.

13.5 APPENDIX E

AMENDMENTS TO THE PROTOCOL

Revisions to the protocol after initial IRB approval are summarized in the amendment below.

Amendment	Date
1	2/24/2016

The following revisions were made to the protocol dated 02/10/2016.

- Removed Day 7 visit and adjusted visit numbers for Day 14 and Day 29 accordingly. References to all visit numbers were updated throughout the protocol to reflect this 3-visit schedule.
- "None" added to Ocular Discomfort ratings.
- Formatting and administrative changes throughout protocol.

Amendment	Date
2	5/31/2016

The following revisions were made to the protocol dated 02/24/2016.

- Primary endpoint definition revised per FDA advice letter for IND 124879 dated 04/07/2016.
- Added language to clarify that CMH test will be stratified by clinical site.
- Sample size determination wording and study power revised.
- Revised primary analysis to use imputation method for missing data.
- Added language to clarify when dosing should begin relative to randomization.
- Study restrictions revised to allow OTC topical products for the treatment of body psoriasis.
- Formatting and administrative corrections throughout the protocol.