1.0 TITLE PAGE

Drug Product	Desoximetasone Spray, 0.15%
Population	Up to 120 patients (12 years of age and older) with mild to moderate plaque psoriasis
Study Design	Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Clinical Study
Sponsor	Taro Pharmaceuticals U.S.A., Inc. 3 Skyline Drive, Hawthorne, NY 10532
Protocol Number	DSXS 1505
Novum Study Number	71542603
Protocol Date	02/15/17

NIIRB
February 21, 2017
APPROVED

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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 and Data Management
Novum Pharmaceutical Research Services

2/22/17
Date

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Medical Monitor
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9 March 2017
Date

PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol DSXS 1505 Rev. 5 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, U.S.A., Inc.) or Novum Pharmaceutical Research Services, the company managing the study.

_____ _____

Principal Investigator Date

3.0 TABLE OF CONTENTS

4.0 SYNOPSIS

Protocol Number	71542603
Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Clinical Study to Evaluate the Efficacy and Safety of Desoximetasone Topical Spray, 0.15% (Taro Pharmaceuticals, U.S.A., Inc.) in Patients with Mild to Moderate Plaque Psoriasis
Objectives	To evaluate the therapeutic efficacy and safety of desoximetasone topical spray, 0.15% (Taro Pharmaceuticals, U.S.A., Inc.) compared to a Placebo (vehicle) spray (Taro Pharmaceuticals, U.S.A., Inc.) in patients with mild to moderate plaque psoriasis
Sponsor	Taro Pharmaceuticals, U.S.A., Inc.
Study Products	• **Test:** Desoximetasone topical spray, 0.15% (Taro Pharmaceuticals, U.S.A., Inc.) • **Placebo:** Vehicle spray (Taro Pharmaceuticals, U.S.A., Inc.)
Route of Administration	Topical
Treatment Randomization	1:1 (Test: Placebo)
Patient Population	Up to 120 male and non-pregnant females, 12 years of age or older, with a confirmed diagnosis of mild to moderate plaque psoriasis will be enrolled to provide for up to 60 patients per each treatment group (Test or Placebo). Enrollment will begin with the 18 and older population. Enrollment for patients 12-17 will begin once we have safety data from the Phase 2 study has be reviewed.
Study Design	Randomized, double-blind, placebo-controlled, multiple-site, parallel design
Study Conduct	Eligible patients will be randomized in a 1:1 ratio to Test or Placebo product. Patients will complete 4 clinic visits over a 4 week study duration as follows: • **Visit 1:** Randomization (Day 1), • **Visit 2:** Interim Visit (Day 7 ± 2), • **Visit 3:** Interim Visit (Day 14 ± 2), • **Visit 4:** End of Treatment (Day 28 ± 2). Patients will be contacted at Day 42 ± 4 (Visit 5) for a Telephone Follow-up to report any Adverse Events that have occurred since the end of treatment, Therapeutic efficacy evaluation will be based on clinical assessment of plaque psoriasis by the Investigator. Such clinical assessment will include scoring of the severity of signs and symptoms of plaque psoriasis. Refer to Appendices A, B and C for body surface area (BSA) estimation,

	Investigator's Global Assessment Scale (IGA), Total Lesion Severity Score (TLSS) and Psoriasis Area Severity Index (PASI), respectively.
Inclusion Criteria	1. Male or non-pregnant, non-lactating female 12 years of age or older. 2. Signed informed consent form (ICF), which meets all criteria of current. FDA regulations. For patients under the age of majority in the state the study is being conducted (18 years in most states) the parent or legal guardian should sign the consent form and the child will be required to sign a patient "assent" form that will be written in such a way as to be understandable to a child. 3. If female and of child-bearing potential, prepare to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g., condom + spermicide, IUD, oral, transdermal, injected or implanted hormonal contraceptives). 4. Have a definite clinical diagnosis of stable plaque psoriasis involving 5-10% of the body surface area (BSA). Refer to Appendix A. 5. Have a plaque elevation score of ≥ 2 (mild) for the Target Lesion (based on TLSS, Appendix B). 6. The Target Lesion must have an area of at least 5 cm^2. 7. Have a Investigator's Global Assessment (IGA) score of 2 (mild) or 3 (moderate) at baseline for the overall disease severity (Appendix C). 8. Target Lesion must not be on the face, genitals, or intertriginous area (i.e., breast fold, gluteal crease, axilla, etc.).
Exclusion Criteria	1. Patient is < 12 years old. 2. Female who is pregnant, nursing, planning to become pregnant during the duration of the study, or if of child-bearing potential and sexually active and not prepared to use appropriate contraceptive methods to avoid pregnancy. 3. Has less than 5% or greater than 10% of BSA affected with plaque psoriasis. 4. A score of < 2 (mild) for the individual sign of plaque elevation for the Target Lesion (based on TLSS, Appendix B). 5. Target Lesion area less than 5 cm^2. 6. Investigator's Global Assessment (IGA) Score < 2 (mild) or > 3 (moderate) at baseline for the overall disease severity.

	7. Patient has current diagnosis of other types of psoriasis other than stable plaque psoriasis (i.e. acute, guttate, erythrodermic, exfoliative or pustular psoriasis) or has psoriasis of any kind of the face or scalp that will require active treatment during the study. Nonprescription antipsoriatic shampoos will be allowed during the study when applied solely to the scalp. 8. Patient presents active cutaneous bacterial or viral infection at baseline and/or skin atrophy in ant treatment area. 9. Patient has a history of psoriasis that has been unresponsive to topical corticosteroid therapy. 10. In the Investigator's opinion, the patient has other dermatological conditions, such as atopic or contact dermatitis, that may interfere with the clinical assessments of the signs and symptoms of psoriasis. 11. Patient has a history of allergy or sensitivity to corticosteroids or history of any drug hypersensitivity or intolerance which, in the opinion of the Investigator, would compromise the safety of the patient or the results of the study. 12. Patient has a 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 patient at undue risk by participation in the study. 13. Patient is currently receiving or has received any radiation therapy, anti-neoplastic agents or immunosuppressant medication within 4 weeks before the first dose of study drug. 14. Patient has undergone treatment with any systemic or photo antipsoriatic therapy within 8 weeks of the first dose of study drug. 15. Patient has been treated within 12 weeks (or five half lives, whichever is less) before the first dose of study drug with any biological therapies for psoriasis. 16. Patient has received any systemic steroids within 4 weeks of the first dose of the study drug. The use of inhaled or intranasal corticosteroids is acceptable as long as usage has been stable for at least 2 weeks before the first dose of study drug and will be continued during the study. 17. Females using hormonal contraceptives for less than one complete cycle before entering the study. 18. Patients who have used any topical anti-psoriatic agents of any kind or any topical corticosteroids for any reason within 2 weeks before first use of study drug. Nonprescription anti-psoriatic shampoos used only on the

	scalp will be allowed during the study. 19. Receipt of any drug as part of a research study within 30 days before first dosing. 20. In the opinion of the Investigator, the patient will not be compliant with the requirements of the study procedures. 21. Previous participation in this study.
Efficacy Endpoints	**<u>Primary Efficacy Endpoints</u>** 1. The proportion of patients in each treatment group who are considered a Clinical Success at Day 28 ± 2 (i.e., at least a 2-grade improvement from the patient's baseline IGA score) 2. The proportion of patients in each treatment group who are considered a Treatment Success for the Target Lesion at Day 28 ± 2 (i.e., a TLSS value of 0 or 1 at Day 28 ± 2 for each of the three signs and symptoms (i.e., erythema, scaling and plaque elevation) depending on the patient's baseline TLSS) **Definitions:** 1. <u>Treatment Success:</u> To be considered a Treatment Success the patient's TLSS value at Day 28 ± 2 must be 0 if their baseline TLSS value is 2 and must be 0 or 1 if their baseline TLSS value is > 2 for each of the individual signs and symptoms 2. <u>Treatment Failure:</u> A patient will be considered a Treatment Failure if: a. the patient's TLSS value is > 0 if their baseline TLSS value is 2 or > 1 if their baseline IGA score is > 2 for any of the individual signs and symptoms b. the patient was considered to have an insufficient therapeutic response 3. <u>Clinical Success:</u> To be considered a Clinical Success the patient must have at least a 2-grade improvement from their baseline IGA score. That is, an IGA score of 0 at Day 28 ± 2 if their baseline IGA score is 2 or an IGA score of 0 or 1 at Day 28 ± 2 if their baseline IGA score is 3 4. <u>Clinical Failure:</u> A patient will be considered a Clinical Failure if: a. the patient's IGA score is > 0 if the baseline IGA score is 2 or > 1 if the baseline IGA score is 3 b. the patient was considered to have an insufficient therapeutic response

	Secondary Efficacy Endpoints The secondary efficacy endpoints are: 1. The proportion of patients with a baseline IGA score of 3 who are considered a Clinical Success. 2. The proportion of patients with a baseline IGA score of 3 who are considered a Treatment Success. 3. The proportion of patients with a baseline IGA score of 2 who are considered a Clinical Success. 4. The proportion of patients with a baseline IGA score of 2 who are considered a Treatment Success. 5. The change from baseline in %BSA affected at Day 28 ± 2
Therapeutic Efficacy Analysis	**Primary Efficacy Analyses** The Test treatment will be compared with Placebo for each primary endpoint at the 5% significance level ($p < 0.05$; two-sided, Cochran-Mantel-Haenszel exact test) in the intent-to-treat (ITT) population using last observation carried forward (LOCF). As this is a multiple-site study, the interaction of treatment-by-site may be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ($p < 0.05$) for the primary efficacy variable in the ITT population for superiority testing. Superiority of Test over Placebo will be demonstrated if both dichotomous endpoints show statistical significance at the 5% significance level. For sensitivity testing, the primary analysis will also be performed using the per protocol (PP) population. **Secondary Efficacy Analyses** The Test treatment will be compared with Placebo for each dichotomous secondary endpoint at the 5% significance level ($p < 0.05$; two-sided, Cochran-Mantel-Haenszel exact test) in the ITT population using LOCF. The Test treatment will be compared with Placebo for the continuous secondary endpoint at the 5% significance level in the ITT population using last observation carried forward (LOCF). Analysis of Covariance (ANCOVA) will be used for the evaluation of the continuous secondary endpoint using baseline %BSA as a covariate. For the secondary efficacy analyses, superiority of Test over Placebo will be considered supported for each endpoint if the difference is statistically significantly greater than 0 at the 5% significance level. There will be no multiplicity adjustment for the evaluation of the five secondary endpoints. Descriptive statistical analysis will be generated to compare the efficacy results in each treatment group at each visit.

Safety Analysis	Adverse events (AEs) will be classified using standard MedDRA terminology Version 17.0 or higher and summarized by treatment group. Summary tables comparing the type, incidence, severity will be prepared by treatment group. The relationship of AEs, if any, to the study drug will be assessed by the Investigator. All AEs will be presented regardless of suspected causality. The frequency, severity and relationship to study drug for AEs in each treatment group will be used to evaluate the safety profile of the test product.
Sample Size Determination	The primary analyses of interest are the proportion of patients in the Test and Vehicle treatment groups who are considered to be a Clinical Success and Treatment Success on Day 28. In-house data from two Phase III studies that evaluated the safety and efficacy of desoximetasone spray 0.25% (twice daily for 28 days) in patients with moderate to severe plaque psoriasis were used for sample size determination. These studies were conducted in support of Taro's NDA #204141, Topicort® (desoximetasone) Topical Spray, 0.25%. In those studies the Clinical Success rates were 31% and 53% for the active product (42% average) and 5% and 18% for the vehicle treatment (12% average), and the Treatment Success rates were 39% and 53% for the active product (46% average) and 7% and 17% for the vehicle treatment (12% average). Based on the average results from these two studies on the 0.25% spray, the proportion of subjects in the Test group considered a Clinical Success and Treatment Success is expected be 40% or higher and the proportion of subjects in the Vehicle group considered a Clinical Success and Treatment Success is expected to be 12% or less for desoximetasone spray 0.15% in patients with mild to moderate plaque psoriasis. With these assumptions, 50 evaluable subjects in the ITT in each treatment group will demonstrate superiority of the Test to the Vehicle group with 89% power at the 5% level of significance ($p < 0.05$, using two-sided *Z*-test), assuming 100% correlation between Clinical and Treatment Success rates. To allow for patients who may drop out from the study or are otherwise non-evaluable, up to 120 patients may be enrolled (60 in the Test group and 60 in the Vehicle group).

5.0 STUDY SCHEMATIC

PROCEDURE	VISIT 1 Randomization Day 1	VISIT 2 Interim Visit Day 7 ± 2 days	VISIT 3 Interim Visit Day 14 ± 2 days	VISIT 4 End of Treatment Day 28 ± 2 days	VISIT 5 Telephone Follow-Up Visit Day 42 ± 4 days
Informed Consent	X				
Medical History & Demographics	X				
Height and Weight	X				
Vital Signs	X	X	X	X	
Dermatological Assessment	X	X	X	X	
% BSA Assessment	X	X	X	X	
IGA Score	X	X	X	X	
Total Lesion Severity Score	X	X	X	X	
PASI Score	X	X	X	X	
Application Site Reactions	X	X	X	X	
Target Lesion Photograph**	X	X	X	X	
Pregnancy Test*	X			X	
Concomitant Medication	X	X	X	X	
Collect/Dispense Study Medication	X		X	X	
Provide/Review patient Dosing Diary	X	X	X	X	
Adverse Events		X	X	X	X
Evaluation of Patient Compliance to the Protocol		X	X	X	

* Pregnancy Test will be conducted for women of child-bearing potential

** Selected sites will be designated to take photographs of a defined target lesion at each Clinic Visit

6.0 LIST OF ABBREVIATIONS AND TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BSA	Body Surface Area
C	Celsius
CRF	Case Report Form
CRO	Clinical Research Organization
eCTD	electronic Common Technical Document
FDA	Food and Drug Administration
HPA	Hypothalamic Pituitary Adrenal
HRT	Hormone Replacement Therapy
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
OHRP	Office of Human Rights Protection
OTC	Over The Counter
PASI	Psoriasis Area Severity Index
PP	Per-Protocol
SAE	Serious Adverse Event
TLSS	Total Lesion Severity Score
U.S.A.	United States of America

7.0 INTRODUCTION

7.1 Disease Being Treated

Psoriasis is an immune (T-cell)-mediated inflammatory skin disease that affects approximately 2% of the western population.[1] 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]

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.[4,5] Investigator's Global Assessment (IGA) is also one of the preferred methods of clinical evaluation of the severity and extent of psoriasis. [2,4,5]

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. Psoriasis treatments historically include topical creams, sprays, lotions, foams. Examples of marketed products include corticosteroids (Topicort®, Clobex™), Vitamin A & 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. [2,6,7]

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) Topical 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.

A new formulation; desoximetasone topical spray, 0.15% has been developed by Taro Pharmaceuticals U.S.A., Inc., and is the Test product used in this study.

7.3 Scientific and Statistical Considerations

Taro Pharmaceuticals USA, Inc. has developed and marketed Topicort ® (desoximetasone 0.25%) topical spray, and Topicort ® (desoximetasone 0.25% & 0.05%) topical creams,

for the treatment of plaque psoriasis.[8] 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.[1,2,6,7,9]

The design for this study is based on results from Phase II dose-ranging and Phase III efficacy studies (NDA # 204141) conducted for Topicort® (desoximetasone) 0.25% topical spray (Taro Pharmaceuticals U.S.A., Inc.).[10,11] The primary efficacy endpoints (Clinical Success and Treatment Success) are based on these studies as well as those reported in the NDA (# 021835) for the marketed product, Clobex® (clobetasol) 0.05% spray.[12]A sample size estimation of 120 enrolled patients (60 patients per treatment group, 1:1 ratio) is based on the assumption that ≥ 40% of patients receiving Test (active) treatment, and ≤ 12% of patients receiving Placebo (vehicle) treatment will have Clinical Success and Treatment Success.

Statistical analyses of the clinical data will be based on FDA guidances and any communications with FDA on how they would like such data analyzed.

7.4 Justification for use of Placebo

Based on recommendations from FDA, ICH and the guidebook to Institutional Review Boards (IRBs) issued by the Office of Human Rights Protection (OHRP), a Division of the United States Federal Government's Department of Health and Human Services, a Placebo 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 containing no active ingredient to treat plaque psoriasis.[13,14]

7.5 Risks and Benefits

According to recommendations from the IRB guidebook referenced above, the risks and benefits to patients enrolled in clinical research studies that include a placebo treatment group must be carefully considered based on three main criteria, namely: the disease being treated, the availability, efficacy and safety of approved therapies and the scientific and statistical requirements of the desired outcome of the research study. Qualified patients entering the active treatment period have a 50% chance of receiving Placebo. 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 Placebo 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.

Desoximetasone is a high potency synthetic corticosteroid marketed in a number of formulations: gel (0.05%), cream (0.05% and 0.25%), ointment (0.05% and 0.25%)

indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 18 years and older. In 2013 a new dosage form (spray) received the FDA approval under NDA #204141, Topicort® (desoximetasone) Topical Spray, 0.25%, a super high potency formulation that is indicated for the treatment of plaque psoriasis in patients 18 years of age and older. The new product does not pose a safety concern in patients 18 years and older because the concentration of desoximetasone in the new formulation of desoximetasone spray 0.15% does not exceed concentrations of the marketed products. The study enrollment will be initiated for patients 18 years of age and older. The enrollment for younger patients will be open after completion of the corresponding age cohort in the safety study to assess the potential for adrenal suppression following maximal use treatment.

8.0 STUDY OBJECTIVE

To evaluate the therapeutic efficacy and safety of desoximetasone topical spray, 0.15% (Taro Pharmaceuticals, U.S.A., Inc.) compared to a Placebo (vehicle) spray (Taro Pharmaceuticals, U.S.A., Inc.) in patients with mild to moderate plaque psoriasis.

9.0 INVESTIGATIONAL PLAN

9.1 Study Design and Plan Description

This double-blind, randomized, placebo-controlled, parallel group, multi-site study is designed to evaluate the therapeutic efficacy and safety of desoximetasone topical spray, 0.15% (Taro Pharmaceuticals, U.S.A., Inc.).

Up to 120 patients will be enrolled to randomize up to 60 patients in the Test group and 60 in the Placebo group. Before any study-specific procedures are performed all patients will read and sign the IRB-approved informed consent form. In addition, patients considered as minors by the state law in which the clinical site is located (in most States under 18 years of age), must have a signed parental/guardian Informed Consent Form (ICF), indicating approval to participate, as well as a signed assent to participate form.

To qualify for inclusion in the study, patients must be at least 12 years of age with a confirmed diagnosis of mild to moderate plaque psoriasis and must fulfill the following primary inclusion criteria:

- An affected BSA of 5 - 10% (Appendix A)
- A IGA score of 2 (mild) or 3 (moderate) (Appendix B)
- Target Lesion area of at least 5 cm^2
- Plaque Elevation Score ≥ 2 for the Target Lesion (based on TLSS score, Appendix B)

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

- **Test:** Desoximetasone topical spray, 0.15% (Taro Pharmaceuticals, U.S.A., Inc.)
- **Placebo:** Vehicle spray (Taro Pharmaceuticals, U.S.A., Inc.)

Randomized study medication will be self-administered by the patient for 28 days. Patients will be instructed to spray the study medication directly to all affected areas and gently and completely rub in the study drug twice a day for 28 days. Study medication will be applied in the morning and evening approximately 12 hours apart. Patients will return to the clinic at scheduled Visits 2, 3 and 4. Each patient will be provided with a dosing diary in which they will be required to record dosing dates and times. These diaries should be brought to each visit so that the study staff may check compliance. At the end of the study, the dosing diaries will be retained in the patient's file as source documentation.

During the study patients will visit the research center for a total of 4 scheduled visits:

- **Visit 1:** Randomization (Day 1),
- **Visit 2:** Interim Visit (Day 7 ± 2),
- **Visit 3:** Interim Visit (Day 14 ± 2),
- **Visit 4:** End of Treatment (Day 28 ± 2).

Patients will be contacted at Day 42 ± 4 (Visit 5) for a Telephone Follow-up to report any Adverse Events that have occurred since the end of treatment,

Evaluation of therapeutic efficacy will be primarily based on dermatological evaluation of psoriasis. The evaluation will include scoring of the extent and severity of plaque psoriasis. Refer to Appendices A, B and C for body surface area (BSA) estimation, Investigator's Global Assessment Scale (IGA), Total Lesion Severity Score (TLSS) and Psorasis Area Score Index (PASI), respectively. Selected sites will be instructed to take photographs of a target lesion at each visit.

9.2 Selection of Study Design

The study design is primarily based on Phase III efficacy studies (NDA#204141) conducted for Topicort® (desoximetasone) 0.25% topical spray (Taro Pharmaceuticals U.S.A., Inc.) and communications between Taro Pharmaceuticals, U.S.A., Inc. and the FDA regarding the scope and design of clinical studies for desoximetasone topical spray, 0.15%. The study also follows recommendations provided in the FDA guidance document for topical dermatological products, and information available from published clinical trials in plaque psoriasis.[4,7,10,11,13,15]

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Male or non-pregnant, non-lactating female 12 years of age or older.
2. Signed informed consent form (ICF), which meets all criteria of current FDA regulations. For patients under the age of majority in the state the study is being conducted (18 years in most states) the parent or legal guardian should sign the consent form and the child will be required to sign a patient "assent" form that will be written in such a way as to be understandable to a child.
3. If female and of child-bearing potential, prepare to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g., condom + spermicide, IUD, oral, transdermal, injected or implanted hormonal contraceptives).
4. Have a definite clinical diagnosis of stable plaque psoriasis involving 5-10% of the body surface area (BSA). Refer to Appendix A.
5. Have a plaque elevation score of ≥ 2 (mild) for the Target Lesion (based on TLSS score, Appendix B).
6. The Target Lesion must have an area of at least 5 cm^2.
7. Have a Investigator's Global Assessment (IGA) score of 2 (mild) or 3 (moderate) at baseline for the overall disease severity (Appendix C).
8. Target Lesion must not be on the face, genitals, or intertriginous area (i.e., breast fold, gluteal crease, axilla, etc.).

9.3.2 Exclusion Criteria

1. Patient is < 12 years old.
2. Female who is pregnant, nursing, planning to become pregnant during the duration of the study, or if of child-bearing potential and sexually active and not prepared to use appropriate contraceptive methods to avoid pregnancy.
3. Has less than 5% or greater than 10% of BSA affected with plaque psoriasis.
4. A score of < 2 (mild) for the individual sign of plaque elevation for the Target Lesion at screening.
5. Target Lesion area less than 5 cm^2 at screening.
6. Investigator's Global Assessment (IGA) Score < 2 (mild) or > 3 (moderate) at screening for the overall disease severity.
7. Patient has current diagnosis of other types of psoriasis other than stable plaque psoriasis (i.e., acute, guttate, erythrodermic, exfoliative or pustular psoriasis) or has psoriasis of any kind of the face or scalp that will require

active treatment during the study. Nonprescription antipsoriatic shampoos will be allowed during the study when applied solely to the scalp.

8. Patient presents active cutaneous bacterial or viral infection at baseline and/or skin atrophy in ant treatment area.
9. Patient has a history of psoriasis that has been unresponsive to topical corticosteroid therapy.
10. In the Investigator's opinion, the patient has other dermatological conditions, such as atopic or contact dermatitis, that may interfere with the clinical assessments of the signs and symptoms of psoriasis.
11. Patient has a history of allergy or sensitivity to corticosteroids or history of any drug hypersensitivity or intolerance which, in the opinion of the Investigator, would compromise the safety of the patient or the results of the study.
12. Patient has a 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 patient at undue risk by participation in the study.
13. Patient is currently receiving or has received any radiation therapy, anti-neoplastic agents or immunosuppressant medication within 4 weeks before the first dose of study drug.
14. Patient has undergone treatment with any systemic or photo antipsoriatic therapy within 8 weeks of the first dose of study drug.
15. Patient has been treated within 12 weeks (or five half lives, whichever is less) before the first dose of study drug with any biological therapies for psoriasis.
16. Patient has received any systemic steroids within 4 weeks of the first dose of the study drug. The use of inhaled or intranasal corticosteroids is acceptable as long as usage has been stable for at least 2 weeks before the first dose of study drug and will be continued during the study.
17. Females using hormonal contraceptives for less than one complete cycle before entering the study.
18. Patients who have used any topical anti-psoriatic agents of any kind or any topical corticosteroids for any reason within 2 weeks before first use of study drug. Nonprescription anti-psoriatic shampoos used only on the scalp will be allowed during the study.
19. Receipt of any drug as part of a research study within 30 days before first dosing.

20. In the opinion of the Investigator, the patient will not be compliant with the requirements of the study procedures.
21. Previous participation in this study.

9.3.3 Restrictions during the Study

The following concomitant medications will not be allowed while enrolled in the study:

- Any prescription or OTC topical, systemic, phototherapy or biological medications or treatments for psoriasis.
- Application of any emollient on the treatment area.
- Any non-steroidal immunosuppressants (by any route of administration).
- Use of non-sedating anti-histamines.
    - The use of sedating anti-histamines, such as diphenhydramine, may be acceptable on condition the patient has been on a stable dose for at least 14 days before enrollment and will remain on a stable dose throughout the study.
- Any oral, topical or injectable steroid drug use (with the exception of HRT and contraceptives).
    - Female patients using hormonal contraceptives or HRT should have been on the same product/dosing regimen for at least 4 weeks before and should not change this during the study.
- New regimens of inhaled corticosteroids.
    - Inhaled or intranasal corticosteroids are permissible, provided that the patient has been on a stable regimen for at least 2 weeks before the first dose of study drug and will continue during the study.
- Any other treatments, prescription or over-the-counter products for the treatment of any other dermatological condition including; topical corticosteroids**,** antibacterial, medicated and/or astringent washes, soaps, pads or moisturizers during the study.
- Use of high strength (20% or above) alpha-hydroxy acid or any kind of peel or other procedures on the treatment areas (laser hair removal) during the study.

Patients will be advised to avoid environmental conditions that may exacerbate their disease state. Patients will be advised to avoid exposure to sunlight of a duration that would require application of sunscreen.

Patients will be advised not to cover the skin being treated with bandages, dressings or wraps that will occlude the treatment area.

Patients will be questioned about all concomitant prescription and OTC medication use at each study visit. All concomitant medications will be recorded in the patient's study chart. Any patient who violates any of the listed restrictions may be dropped from continued participation in the study by the Investigator.

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. A patient may also be withdrawn for not complying with study procedures. The clinical report will include all reasons for early withdrawals.

Reasons for removal may include the following:

- Worsening signs/symptoms.
- 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.
- Signs and symptoms of possible hypothalamus-pituitary axis (HPA) axis suppression.
- 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 Visit 4 study procedures. In case of early termination the Investigator shall fully document the reason for early termination.

Patients who discontinue early or who significantly deviate from the protocol will be included in the intent-to-treat (ITT) population with LOCF.

9.4 Treatments

The following treatments will be used in the study:

- **Test:** Desoximetasone topical spray, 0.15% (Taro Pharmaceuticals, U.S.A., Inc.), applied twice a day for 28 days
- **Placebo:** Vehicle spray (Taro Pharmaceuticals, U.S.A., Inc.) applied twice a day for 28 days

9.4.1 Treatments Administration

An Independent Dispenser will dispense the study medication and provide instruction on the dosing technique. The patient will be told to spray and gently rub in the study drug (until it is completely absorbed into the skin) to the affected areas twice a day (morning and evening), approximately 12 hours apart, for 28 days. To ensure compliance with the dosing technique, patients will be instructed to apply the medication under the supervision of the Independent Dispenser at the time of enrollment and then twice daily until their next scheduled visit. Patients will be provided with a dosing diary in which they will be required to record dosing dates and times. These diaries should be brought to each visit in order that the study staff may check compliance. At the end of the study, the dosing diaries will be retained in the patient's file as source documentation.

Qualified study patients will be provided with one 100 ml bottle of study medication at Visit 1 along with instructions for dosing. Bottles of study drug should be weighed before dispensing and after they are returned so the weight will be recorded. At Visit 3 (Day 14 ± 2) the first bottle should be collected and new 100 ml bottle of spray should be dispensed along with dosing instructions. This bottle will be returned at Visit 4 (Day 28 ± 2). Based on a maximum of 2 x 3 ml applications/day, 2 x 100 ml bottles of spray should provide sufficient drug for the study. Bottles will be weighed at the time of dispensing and when returned to determine that amount of drug used.

The patient will be informed to avoid smoking and proximity to heat or flame while using the product owing to the flammability of the product.

Treatment compliance will be encouraged by instructing the patient on the proper dosing technique and by the use of the daily diary. Compliance will be assessed by evaluation of the diary and overall exposure to study drug will be assessed by weighing the study drug bottles before and after use (see sections 9.4.5 and 9.6.11).

9.4.2 Identity of Investigational Product

The following products will be used in the study:

- **Test:** Desoximetasone topical spray, 0.15% (Taro Pharmaceuticals, U.S.A., Inc.)
- **Placebo:** Vehicle spray (Taro Pharmaceuticals, U.S.A., Inc.)

Study products will be supplied as 2 x 100 ml bottles of spray.

All randomized study medication will be blinded and packaged in blinded sealed boxes. Study medication and placebo will be packaged in identical, opaque bottles to maintain the study blind. Each bottle will be identified only by a label bearing the Sponsor name, protocol number, randomization number, treatment duration and a statement that the study medication is for Investigational Use Only. The study staff will dispense the study medication bottle only to those patients identified by the Investigator. The study staff will instruct the patients on the use and return of study drug. The patient will be instructed not

to discuss the appearance of the study medication bottle with any study personnel conducting the study visits i.e., the Investigator(s) or the Study Coordinator(s).

Individual boxes containing tubes of study medication will be packaged in blocks. One block will consist of 4 patients' worth of study medication (i.e., 2 x Test: 2 Placebo). The study medication 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 medications are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study medication will be maintained in accordance with federal regulations. Study medication will be stored at controlled room temperature 15-30°C (59-86ºF).

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

9.4.3 Method of Assigning Patients to Treatment Groups

The study drug will be randomized, packaged and blinded by an independent packaging company. Randomization will be pre-planned according to a computer-generated randomization schedule. The randomization will be generated in blocks, each containing 4 patients' worth of medication (2 x Test product and 2 x Placebo). Each patient kit will contain 2 x 100 ml bottles of study medication.

The randomization number will be a unique 4 digit number.

A perforated or two-part label will be attached to the box of drug supplies for each patient. Both pieces of the label should include the following information: protocol number, randomization number, space for patient's initials, statement that the drug is for Investigational Use Only, space for dispensing date, storage information and the Sponsor's name. One part of the label shall remain attached to the box. The other part will be removed before dispensing and attached to the patient's source documents.

At the end of the study, after all the clinical data have been entered and the study database has been locked, a copy of the randomization will be sent to the statistician.

9.4.4 Study Blind

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment. To maintain the Investigator-Blind, the Independent Dispenser will be responsible for dispensing and collecting study medication. The patient will be requested not to discuss the appearance of the study medication with the Investigator or study staff.

Each study site will have at least one Independent Dispenser. The role of the Independent Dispenser is to dispense and collect all study medication from the patients and to ensure the study medication logs are completed. They should not be involved in collecting any efficacy data in the study thus ensuring the integrity of the study blind.

To ensure information that could potentially bias handling of data is not disclosed, the clinical packaging company will hold the randomization scheme until database lock. For each patient an individual code break card describing the actual treatment will be provided with the study medication, to be unblinded only in the case of medical emergency and should be kept at the site with the study documents when the study is completed. Whenever possible, the Novum Medical Monitor must be contacted before breaking the blind for any patient. The code break cards should be stored in a secure location at all times and maintained at the site for all randomized patients after the completion of the study.

At the conclusion of the study, after the database has been locked, each site will be sent an envelope containing the full study randomization scheme that should be retained with the study documents in case needed during an FDA Inspection.

9.4.5 Compliance

Patients will be provided with a diary to record the time and date of dosing, other concomitant medications and adverse events. Patients taking fewer than 75% or more than 125% of the required doses, or who missed scheduled applications for > 3 consecutive days will be considered non-compliant with dosing. Compliance with dosing will be verified by the use of the patient diaries.

9.5 Study Conduct

9.5.1 Visit 1 (Day 1): Randomization

1. **Informed Consent/Assent**: Patients who are willing to comply with study procedures will read and sign the informed consent/assent. Patients under the age of majority will read and sign the assent to participate form and their parent or legal guardian must sign the consent form.
2. **Medical History**: Review the patient's demographic and medical history.
3. **Height/Weight and Vital Signs**: The patient's height (meters) and weight (kg) will be measured. The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
4. **Dermatological Assessment**: Clinical signs and symptoms of psoriasis will be evaluated by the Investigator based on the following:
    - % BSA assessment (Appendix A)

- IGA Score (Appendix C)
- TLSS Score (Appendix B)
- PASI Score (Appendix D)
- Application Site Reactions (Appendix E)

5. **Pregnancy Test**: A pregnancy test will be required of all female patients of childbearing potential before enrollment.
6. **Concomitant Medication**: Review the patient's use of concomitant medication within the last 12 weeks.
7. **Inclusion/Exclusion Criteria**: Confirm that the patient meets all inclusion/exclusion criteria.
8. **Dispense Study Product**: The Independent Dispenser will weigh and dispense one bottle of study drug to eligible patient with instructions. The first dose of study medication should be administered at the site, under supervision, during this visit.
9. **Provide Dosing Diary**: Provide Diary with instructions for dosing and completing the diary.
10. Schedule Visit 2.

9.5.2 Visit 2 (Day 7 ± 2): Interim Visit

1. **Vital Signs**: The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
2. **Dermatological Assessment**: Clinical signs and symptoms of psoriasis will be evaluated by the Investigator based on the following:
   - % BSA assessment (Appendix A)
   - IGA Score (Appendix C)
   - TLSS Score (Appendix B)
   - PASI Score (Appendix D)
   - Application Site Reactions (Appendix E)
3. **Concomitant Medication**: Review the patient's use of any new or ongoing concomitant medications since Visit 1.
4. **Adverse Events**: Review and report any AEs since Visit 1.
5. **Diary Review**: Collect and review patient's dosing diary for compliance and provide new diary.
6. Schedule Visit 3.

9.5.3 Visit 3 (Day 14 ± 2): Interim Visit

1. **Vital Signs**: The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
2. **Dermatological Assessment**: Clinical signs and symptoms of psoriasis will be evaluated by the Investigator based on the following:
    - % BSA assessment (Appendix A)
    - IGA Score (Appendix C)
    - TLSS Score (Appendix B)
    - PASI Score (Appendix D)
    - Application Site Reactions (Appendix E)
3. **Concomitant Medication**: Review the patient's use of any new or ongoing concomitant medications since Visit 2.
4. **Adverse Events**: Review and report any AEs since Visit 2.
5. **Collect Study Product**: The first bottle of study product will be collected and weighed.
6. **Diary Review**: Collect and review patient's dosing diary for compliance and provide new diary.
7. **Dispense Study Product**: Independent Dispenser will weigh and dispense a new bottle of study product corresponding to the patient's randomization number.
8. Schedule Visit 4.

9.5.4 Visit 4 (Day 28 ± 2): End of Treatment

1. **Vital Signs**: The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
2. **Dermatological Assessment**: Clinical signs and symptoms of psoriasis will be evaluated by the Investigator based on the following:
    - % BSA assessment (Appendix A)
    - IGA Score (Appendix C)
    - TLSS Score (Appendix B)
    - PASI Score (Appendix D)
    - Application Site Reactions (Appendix E)
3. **Pregnancy Test**: A pregnancy test will be required of all female patients of childbearing potential at the last study visit.

4. **Concomitant Medication**: Review the patient's use of any new or ongoing concomitant medications since Visit 3.
5. **Adverse Events**: Review and report any AEs since Visit 3.
6. **Evaluation of Patient Compliance to the Protocol**: Independent dispenser will collect and review patient's dosing diary and record total number of doses administered since Visit 3.
7. **Collect Study Product**: The second bottle of study product will be collected and weighed.
8. **Diary Review**: Collect and review patient's dosing diary for compliance.
9. **Discharge**: Review completeness of all source documents for patient and discharge from the study.

9.5.5 Visit 5 (Day 42 ± 4): Follow-up Phone Call

A phone call will be conducted approximately 14 days after the subject has completed dosing to follow-up on any new adverse events that may have occurred.

9.6 Study Procedures

9.6.1 Informed Consent

At Visit 1, before performing any study-related procedures the study patient must sign the IRB-approved consent form. If the patient is under the age of majority in the state that the study is being conducted (18 years in most states) then patient's parent or legal guardian must sign the consent form and the patient must sign the assent form. Both the consent and assent forms 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/assent. 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.

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 psoriasis history and all medication use within the previous 12 weeks.

9.6.4 Vital Signs

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

9.6.5 Height and Weight

At Visit 1 the subject's body weight (kg) and height (cm) will also be measured while the Subject is lightly clothed (e.g., no coat or shoes). The patient's BSA will be calculated using instructions in Appendix A.

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, 3 and 4.

9.6.7 Pregnancy Test

All females of childbearing potential will have a urine pregnancy test performed at Visits 1 and 4. The test must be negative at Visit 1 for the patient to be eligible for inclusion in the study. If the patient is female and not considered of childbearing potential, then the reason must be documented in the patient's source documents.

Any patient who becomes pregnant during the study should be discontinued and end of treatment procedures (Visit 4) completed. The outcome of the pregnancy should be followed by the Investigator to the conclusion of the pregnancy.

9.6.8 Dispensing Study Medication

An Independent Dispenser will dispense study medication at Visit 1, along with dosing instructions. Patients will be instructed to apply the first dose of study medication in the clinic, and the remaining doses at home. The Independent Dispenser will ensure the study medication logs are reported correctly.

9.6.9 Collecting Study Drug

Bottles of study product will be collected at Visit 3 and Visit 4 and checked for compliance or evidence of tampering with the blind.

9.6.10 Dosing Instructions and Diary

Patients will be provided with a dosing diary at Visits 1, 2 and 3 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 reviewed at each visit by the study staff.

9.6.11 Dosing Compliance

Dosing compliance will be checked by site staff at Visits 2, 3 and 4 by reviewing patient diary entries. Patients will be considered compliant with dosing if they administer 75%-125% of the required number of doses, and did not miss more than 3 consecutive days of dosing.

9.6.12 Dermatological Assessment

At Visit 1 a visual inspection to confirm a diagnosis of chronic plaque psoriasis will be performed. At each visit psoriasis will be assessed according to the following measures:

a) % BSA Assessment: Appendix A

b) IGA Score: Appendix C

c) TLSS: Appendix B

d) PASI Score: Appendix D

e) Application Site Reactions: Appendix E

Wherever possible, the same Investigator should attempt to perform all IGA exams at all visits for an individual patient.

During the overall dermatological assessment at Visit 1, the Investigator will determine which lesion in his opinion (considering a combination of size and severity of lesional signs and symptoms) is the most severe. This lesion must have an area of at least 5 cm² and have a plaque elevation score of at least 2 (mild).

This lesion will be designated the Target Lesion. If possible, the Target Lesion should exclude the elbows and knees. The location of the Target Lesion will be identified using an anatomical chart in the source documentation. The size of this lesion (cm²) will be calculated, and the TLSS will be evaluated from this lesion.

To calculate the area of the Target Lesion the Investigator should measure once across its widest point and again at a point midway and perpendicular to the widest point. This should be done using the cm ruler provided. Measurements should be done to the nearest mm and reported in units of cm (i.e., reported as cm out to the first decimal place, not reported nor calculated in mm). These two values should be multiplied to give the total area of the Target Lesion (cm^2).

The Target Lesion should be used for all future evaluations and severity for individual signs and symptoms (scaling, erythema and plaque elevation).

To be eligible for inclusion at Visit 1, the patient must have all of the following:

- An affected BSA of 5 - 10% (Appendix A)
- A IGA score of 2 (mild) or 3 (moderate) (Appendix C)
- Target Lesion area of at least 5 cm²
- Plaque Elevation Score ≥ 2 for the Target Lesion (based on TLSS score, Appendix B)

9.6.13 Health Status/Adverse Events

At Visits 2, 3 and 4 patients will be questioned regarding any changes in their medical status since their previous visit. Any significant changes observed after randomization will be reported as adverse events.

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 17 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.

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 medication 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: 412-291-3171

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 Study Manager:
Danielle Simpson
Coordinator, Clinical Operation
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 analyses of interest are the proportion of patients in the Test and Vehicle treatment groups who are considered to be a Clinical Success and Treatment Success on Day 28.

In-house data from two Phase III studies that evaluated the safety and efficacy of desoximetasone spray 0.25% (twice daily for 28 days) in patients with moderate to severe plaque psoriasis were used for sample size determination. These studies were conducted in support of Taro's NDA #204141, Topicort® (desoximetasone) Topical Spray, 0.25%. In those studies the Clinical Success rates were 31% and 53% for the active product (42% average) and 5% and 18% for the vehicle treatment (12% average), and the Treatment Success rates were 39% and 53% for the active product (46% average) and 7% and 17% for the vehicle treatment (12% average).

Based on the average results from these two studies on the 0.25% spray, the proportion of subjects in the Test group considered a Clinical Success and Treatment Success is expected be 40% or higher and the proportion of subjects in the Vehicle group considered a Clinical Success and Treatment Success is expected to be 12% or less for desoximetasone spray 0.15% in patients with mild to moderate plaque psoriasis. With these assumptions, 50 evaluable subjects in the ITT in each treatment group will demonstrate superiority of the Test to the Vehicle group with 89% power at the 5% level of significance ($p < 0.05$, using two-sided *Z*-test), assuming 100% correlation between Clinical and Treatment Success rates.

To allow for patients who may drop out from the study or are otherwise non-evaluable, up to 120 patients may be enrolled (60 in the Test group and 60 in the Vehicle group).

10.3 Study Populations

10.3.1 Intent-to-Treat (ITT) Population

The ITT population will include:

- All randomized subjects.

Patients discontinued early for any reason will be included in the ITT with their Last Observation Carried Forward (LOCF).

10.3.2 Per-Protocol (PP) Population

The PP population is a sub-population of the ITT population and will include:

- Patients who met all inclusion and exclusion criteria and were randomized according to the randomized treatment assignment.
- Patients who applied at least one dose AND had at least one post-baseline evaluation.
- Patients who were compliant with the dosage regimens following randomization.
- Patients who had no major protocol deviations.

10.3.3 Safety Population

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

10.4 Baseline Comparability

Baseline comparability of all treatment groups will be evaluated separately in the ITT, PP 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)
- Baseline total BSA
- Baseline % BSA affected with psoriasis
- IGA score
- TLSS Score
- PASI Score
- Target Lesion size (area)

Descriptive statistics by treatment group will be presented.

10.5 Efficacy Endpoints

Primary Efficacy Endpoints

1. The proportion of patients in each treatment group who are considered a Clinical Success at Day 28 ± 2 (i.e., at least a 2-grade improvement from the patient's baseline IGA score).
2. The proportion of patients in each treatment group who are considered a Treatment Success for the Target Lesion at Day 28 ± 2 (i.e., a TLSS value of 0 or 1 at Day 28 ± 2 for each of the three signs and symptoms (i.e., erythema, scaling and plaque elevation) depending on the patient's baseline TLSS).

Definitions:

1. Treatment Success: To be considered a Treatment Success the patient's TLSS value at Day 28 ± 2 must be 0 if their baseline TLSS value is 2 and must be 0 or 1 if their baseline TLSS value is > 2 for each of the individual signs and symptoms
2. Treatment Failure: A patient will be considered a Treatment Failure if:
    a. the patient's TLSS value is > 0 if their baseline TLSS value is 2 or > 1 if their baseline IGA score is > 2 for any of the individual signs and symptoms
    b. the patient was considered to have an insufficient therapeutic response
3. Clinical Success: To be considered a Clinical Success the patient must have at least a 2-grade improvement from their baseline IGA score. That is, an IGA score of 0 at Day 28 ± 2 if their baseline IGA score is 2 or an IGA score of 0 or 1 at Day 28 ± 2 if their baseline IGA score is 3
4. Clinical Failure: A patient will be considered a Clinical Failure if:
    a. the patient's IGA score is > 0 if the baseline IGA score is 2 or > 1 if the baseline IGA score is 3
    b. the patient was considered to have an insufficient therapeutic response

Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

1. The proportion of patients with a baseline IGA score of 3 who are considered a Clinical Success.
2. The proportion of patients with a baseline IGA score of 3 who are considered a Treatment Success.
3. The proportion of patients with a baseline IGA score of 2 who are considered a Clinical Success.
4. The proportion of patients with a baseline IGA score of 2 who are considered a Treatment Success.
5. The change from baseline in %BSA affected at Day 28 ± 2 will be evaluated as a secondary endpoint.

10.6 Primary Efficacy Analyses

The Test treatment will be compared with Placebo for each primary endpoint at the 5% significance level ($p < 0.05$; two-sided, Cochran-Mantel-Haenszel exact test) in the ITT population using last observation carried forward (LOCF). Superiority of Test over Placebo will be demonstrated if both dichotomous endpoints show statistical significance at the 5% significance level.

For sensitivity testing, the primary analysis will also be performed using the PP population.

10.7 Secondary Efficacy Analyses

The Test treatment will be compared with Placebo for each dichotomous secondary endpoint at the 5% significance level ($p < 0.05$; two-sided, Cochran-Mantel-Haenszel exact test) in the ITT population using LOCF.

The Test treatment will be compared with Placebo for the continuous secondary endpoint at the 5% significance level in the ITT population using LOCF. Analysis of Covariance (ANCOVA) with treatment and site as fixed effects and baseline %BSA as a covariate in the model will be used for the evaluation of the continuous secondary endpoint.

For the secondary efficacy analyses, superiority of Test over Placebo will be considered supported for each endpoint if the difference is statistically significantly greater than 0 at the 5% significance level. There will be no multiplicity adjustment for the evaluation of the five secondary endpoints.

Descriptive statistical analysis will be generated to compare the efficacy results in each treatment group at each visit.

10.8 Treatment-by-Site Interaction and Pooling of Clinical Sites

As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for superiority testing by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ($p < 0.05$) for the primary efficacy endpoints in the ITT population. A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients at the site with the highest enrolling rate in the ITT population. If no treatment-by-site interaction is identified with the primary endpoints then no adjustment will be made to any efficacy analysis and treatment-by site interaction will not be included as a term in the statistical models for evaluating superiority.

10.9 Safety Analysis

Adverse events (AEs) will be classified using standard MedDRA terminology Version 17.0 or higher and summarized by treatment group. Summary tables comparing the type, incidence, severity will be prepared by treatment group. The relationship of AEs, if any, to the study drug will be assessed by the Investigator. All AEs will be presented

regardless of suspected causality. The frequency, severity and relationship to study drug for AEs in each treatment group will be used to evaluate the safety profile of the test product.

11.0 REGULATORY OBLIGATIONS

11.1 Institutional Review Board

The study protocol, informed consent/assent 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 59th World Medical Association General Assembly, October 2008.[16-18] 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). A set of CRFs will be completed for each patient enrolled in the study. All data and CRFs will be reviewed, evaluated and signed by the Investigator, as required.

The original source documents and a copy of the corresponding CRFs will be retained by the Investigator. Patients who terminate early from the study will have the Visit 4 (end of treatment) source/CRF completed.

11.2.5 Drug Accountability

All drug receipt, inventory, dispensing, dosing and reconciliation records will be maintained in compliance with Federal Regulations. The study drug 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 medication will be returned to Sponsor or designee.

11.2.6 Drug Storage

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

11.2.7 Pregnancies

Patients with a positive pregnancy test during screening 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 Visit 4 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., Norplant®), Depo-Provera®, double barrier methods (e.g., condom and spermicide) or IUD. Before study enrollment women of child bearing 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 Visits 1 and 4 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.

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.[19]

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.[20] 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.

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13.0 APPENDICES

13.1 Appendix A

Total Body Surface Area Calculation

To calculate the Total BSA the following procedure (Mosteller Formula)[21] should be followed.

Total Body Surface Area (BSA) in meters squared

$m^2 = ((\text{height (cm)} \times \text{weight (kg)}) / 3600)^{½}$

Patient's height and weight should preferably be measured in cm and kg however if needed:
To convert inches (in) to centimeters (cm) the following conversion should be used
1 inch = 2.54 cm

To convert pounds (lbs) to kilograms (kg) the following conversion should be used.
1 lb = 0.45 kg

The patient's height and weight should be reported to the nearest cm and nearest 0.5 kg. The BSA should be reported to the nearest second decimal place.

For example a patient who is 68 inches tall and weighs 180 lbs will have a reported BSA of:
68 in x 2.54 = 173 cm
180 lb x 0.45 = 81.0 kg

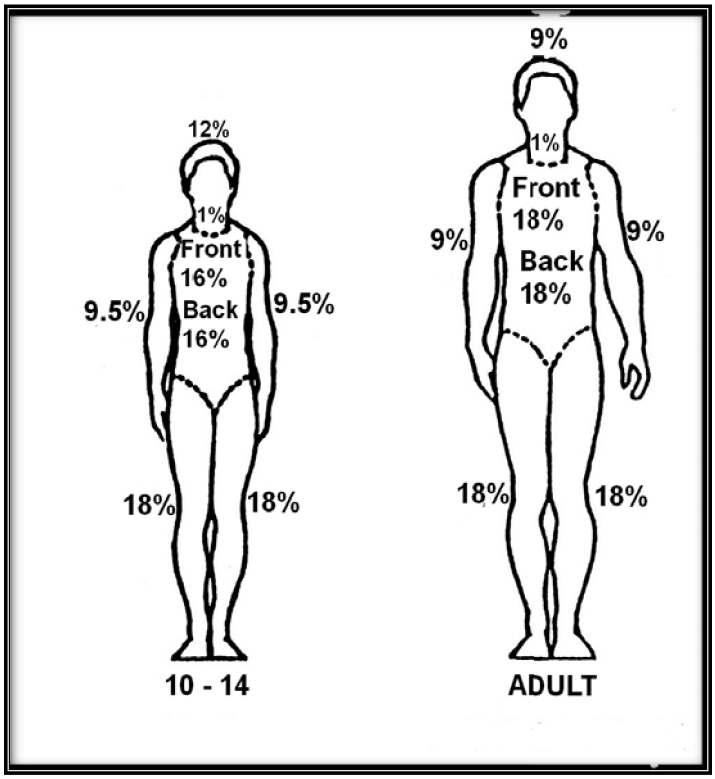
BSA = SQRT ((173 x 81.0)/3600)
= 1.97 m²

%BSA Affected

To calculate the %Body Surface Area Affected the "Rule of Nine" will be used.

Body Surface Area affected will be calculated using the standard medical procedure of the "Rule of Nines". [(5)] The patient's palm surface of the hand represents approximately one percent of his/her body surface area. [(5)] Calculate to the nearest whole percentage.

Part	10-14 year child body % of total	Adult body % of total
Arm	9.5%	9%
Head	12%	9%
Neck	1%	1%
Leg	18%	18%
Anterior trunk	16%	18%
Posterior trunk	16%	18%



To be eligible for inclusion in the study a patient must have a % BSA affected of 5-10%

13.2 Appendix B

TOTAL LESION SEVERITY SCORE (TLSS)

Score	Grade	Erythema	Scaling	Plaque Elevation
0	Clear	No evidence of erythema	No evidence of scaling	No evidence of plaques above normal skin level
1	Almost Clear	Pink discoloration, minimal erythema	Occassional fine scales hardly noticeable	Slight, just discernable elevation above normal skin level
2	Mild	Light red coloration	Slight but definite roughness, fine scale present, no cracking	Discernable elevation above normal skin level upon examination, but not pronounced
3	Moderate	Moderate redness, but not dark	Moderate roughness, somewhat coarse scaling	Definite plaque formation with rounded/sloped edges to plaque
4	Severe	Dark red coloration	Marked roughness, coarse/thick scaling, cracking may be evident	Marked elevation with hard, distinct edges to plaque
5	Very Severe	Very dark red coloration with induration present	Very thick scales covering extensive area, severe cracking/fissures may be evident	Very marked elevation, very hard and sharp edges to plaque

To be considered for inclusion in the study, the Target Lesion must have a minimum plaque elevation score of ≥ 2.

13. 3 Appendix C

INVESTIGATOR'S GLOBAL ASSESSMENT (IGA)

To be eligible for inclusion in the study the IGA must be 2 - 3 at baseline.

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.

13.4 Appendix D

PSORIASIS AREA SEVERITY INDEX (PASI)

The PASI is a composite score based on the severity of three different clinical signs of psoriasis in four different areas of the body multiplied by the percent of that specific body area affected multiplied by a weighting factor.

Erythema, Induration, Scaling will be evaluated using the severity scale below:
0 = Clear
1 = Mild
2 = Moderate
3 = Severe
4 = Very Severe

PASI Score
The PASI score is calculated as follows:

Head/neck	(E + I + S) x Area x 0.1
Upper Limbs	(E + I + S) x Area x 0.2
Trunk	(E + I + S) x Area x 0.3
Lower Limbs	(E + I + S) x Area x 0.4

PASI SCORE = SUM OF ABOVE 4 REGIONS

E: Erythema,
I: Induration
S: Scaling

Severity is based on the Investigator's assessment of individual signs and symptoms
0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe using the definitions above

The % of each body region affected is scored as the variable Area above in the PASI formula. For the 4 body regions (head/neck, upper limbs, trunk and lower limbs) if the:

Area = 0	if % affected is 0%
Area = 1	if % affected is 1 to 9%
Area = 2	if % affected is 10 to 29%
Area = 3	if % affected is 30 to 49%
Area = 4	if % affected is 50 to 69%
Area = 5	if % affected is 70 to 89%
Area = 6	if % affected is 90 to 100%

PASI Score can be presented to the nearest whole number (no decimals and all numbers should be rounded, 0.5 should be rounded up to the nearest whole number). The minimum score would be 0 and the Maximum Score would be 72.

13.5 Appendix E

APPLICATION SITE REACTIONS

The following application site reactions will be evaluated at each visit based on the scale provided below:

Burning

Erosion

Edema

Pain

Itching

Dryness

Absent	0	
Mild	1	(slight, barely perceptible)
Moderate	2	(distinct presence)
Severe	3	(marked, intense)

13.6 Appendix F

Amendments to the Protocol

Revision	Date	
1	07/29/15	

The following revisions were made to the protocol, Revision 0, dated 02/25/15:

- Study schematic was updated to acknowledge that 1 designated site will take photographs of a target area
- The study age range was updated to include patients 12 years of age and older
- Section 7.5 was updated to include justification to begin enrollment in the adult (18 and older) population
- Follow-up phone call (Visit 5) added
- Inclusion Criteria #4 was updated to clarify enrolled of 5-10% BSA affected
- Patient stopping criteria was added to Section 9.7.4
- Section 10.5 was updated regarding the secondary endpoints
- Updates were make to Section 10.6 and 10.7 regarding the Primary and Secondary Analysis
- ITT definitation was revised in Section 10.3.1
- PP Population was added in Section 10.3.2
- TLSS scale added (Appendix B)
- PGA scale was updated to an IGA scale (Appendix C)
- PASI scale was added (Appendix D)
- Application Site Reactions were added to the protocol (Appendix E)

Revision	Date	
2	11/04/15	

The following revisions were made to the protocol, Revision 0, dated 02/25/15:

- Novum address was updated
- A correction was made to section 9.6.8
- Taro SAE contact information was updated

Revision	Date	
3	01/04/16	

The following revisions were made to the protocol, Revision 2, dated 11/04/15:

- Primary efficacy language was updated
- Definition of Clinical Success/Failure and Treatment Success/Failure was updated

Revision	Date	
4	02/24/16	

The following revisions were made to the protocol, Revision 3 dated 01/04/16:

- Minor typographical errors were corrected and clarified

Revision	Date	
5	02/15/17	

The following revisions were made to the protocol, Revision 5, dated 02/24/16:

- Novum and Sponsor representative information was updated.
- Added secondary endpoints and corresponding analysis methods.
- Revised the analysis method for the primary endpoints.
- Corrected minor typographical errors in Appendix D.