1.0 TITLE PAGE

Drug Product	Desoximetasone 0.25% Shampoo, w/w
Design	An open-label, safety study to assess the potential for adrenal suppression following maximal use treatment with desoximetasone 0.25% shampoo applied once-daily in patients with moderate to severe scalp psoriasis
Population	Up to 5-10 patients 12-17 years of age with a confirmed diagnosis of moderate to severe scalp psoriasis with ≥ 20% scalp affected.
Sponsor	Taro Pharmaceuticals U.S.A., Inc. 3 Skyline Drive Hawthorne, NY 10532
Protocol Number	DSXS 1538b
Novum Study Number	71615001
IND #	124879
Protocol Date	04/18/2016
Protocol Rev 1 Date	06/28/2016

2.0 KEY STUDY PERSONNEL AND FACILITIES

Sponsor:	Taro Pharmaceuticals U.S.A., Inc. 3 Skyline Drive Hawthorne, NY 10532
CRO:	Novum Pharmaceutical Research Services (Novum) 225 W. Station Square Drive, Suite 200 Pittsburgh, PA 15219
Sponsor's Representative:	Natalie Yantovskiy Senior Director, Clinical Research Taro Pharmaceuticals U.S.A., Inc. Phone: 914-345-9001 Ext 6849 Fax: 914-593-0078 Email: Natalie.Yantovskiy@Taro.com
CRO representative	Gail Gongas Vice President, Clinical Trials Novum Pharmaceutical Research Services Tel: 412-363-3300 x 522 Fax: 412-924-0522 Email: gdgongas@novumprs.com
Medical Monitor:	Paolo Fanzio, MD Medical Monitor Novum Pharmaceutical Research Services Tel: 412-363-3300 x 597 Fax: 412-291-3171 Email: pmfanzio@novumprs.com
Biostatistician:	Jianhua Liu, MSc Senior Biostatistician Novum Pharmaceutical Research Services Tel: 647-779-6883 Email: jliu@novumprs.com

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

07/14/2016
Date

Paolo Fanzio, MD
Medical Monitor
Novum Pharmaceutical Research Services

07/14/2016
Date

Keith D. Gallicano, PhD
Vice President, Scientific Affairs
Novum Pharmaceutical Research Services

07/26/2016
Date

Natalie Yantovskiy
Senior Director, Clinical Research
Taro Pharmaceutical U.S.A., Inc.

2016.07.27 18:05:26 -04'00'
Date

PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol DSXS 1538b Rev 1 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.) or Novum Pharmaceutical Research Services, the company managing the study.

_____ _____

Principal Investigator Date

3.0 TABLE OF CONTENTS

4.0 SYNOPSIS

Protocol Number	DSXS 1538b
Title	An Open-Label, Safety Study to Assess the Potential for Adrenal Suppression Following Maximal Use Treatment with Desoximetasone 0.25% Shampoo (Taro Pharmaceuticals U.S.A., Inc.) in Patients with Moderate to Severe Scalp Psoriasis
Objectives	The objectives of this study are to: 1. Evaluate the potential of desoximetasone 0.25% shampoo to suppress HPA axis function in patients with moderate to severe scalp psoriasis. 2. Evaluate the efficacy parameters and adverse event (AE) profiles of desoximetasone 0.25% shampoo administered to patients with moderate to severe scalp psoriasis.
Sponsor	Taro Pharmaceuticals U.S.A., Inc.
Name of Test Product	Desoximetasone 0.25% shampoo
Route of Administration	Topical
Study Design	An open-label, safety study to assess the potential for adrenal suppression following maximal use treatment with desoximetasone 0.25% shampoo applied once-daily for 28 days in patients with moderate to severe scalp psoriasis. Each patient is expected to receive 28 doses of study product.
Study Population	Approximately 5-10 male or female patients 12-17 years of age with a confirmed diagnosis of moderate to severe plaque psoriasis of the scalp with ≥ 20% scalp affected.
Study Conduct	All patients will attend the clinic for 3 scheduled visits and a telephone follow-up phone call (Visit 4): **Visit 1:** Screening/Enrollment (Day 1) **Visit 2:** Interim Visit (Day 14 ± 2) **Visit 3:** End of Study (Day 29 ± 2) or Early Termination **Visit 4:** Follow Up (Day 42± 4) Telephone Phone Call If 5 or more patients experience biochemical abnormal values suggestive of possible HPA axis suppression, enrollment will be stopped. Such abnormality is defined by a 30 minute post Cortrosyn™ injection level cortisol level of ≤ 18 mcg/100ml during the Cortisol Response Test.
Inclusion Criteria	1. Male or non-pregnant, non-lactating females 12-17 years of age. 2. If female and of childbearing potential, prepared to abstain from sexual

	intercourse or use a reliable method of contraception during the study (e.g., condom, IUD, oral, transdermal or injected hormonal contraceptives). Female patients using hormonal contraceptives should have been on the same product/dosing regimen for at least 28 days before baseline and should not change this regimen during the study. 3. Signed IRB approved informed consent given by parent(s) or legally acceptable guardian(s) following their receipt of verbal and written information about the study. For patients age 12-17 years of age 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. 4. Patients with a confirmed clinical diagnosis of stable plaque psoriasis of the scalp with ≥ 20% scalp affected. 5. Investigator Global Assessment (IGA) score of 3 (Moderate) or 4 (Severe).
Exclusion Criteria	1. Females who are 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. 2. Patients < 12 years of age or > 17 years of age. 3. Patients whose scalp psoriasis necessitates systemic or other concomitant topical therapies during the study. Concomitant treatment of body psoriasis with OTC topical products, including emollients, is allowed. 4. IGA score < 3. 5. Scalp psoriasis with < 20% scalp affected. 6. History of psoriasis that has been unresponsive to topical corticosteroid therapy. 7. 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). 8. History of an adverse reaction to Cortrosyn™ or similar test reagents 9. 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. 10. 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. 11. Patient has a significant history or current evidence of chronic infectious disease, system disorder, organ disorder or insufficiency, immunosuppression (from medical treatment or disease), organ transplant or other medical condition that, in the Investigator's opinion, would place

	the study patient at undue risk by participation in the study. 12. Patient is currently receiving or has received any radiation therapy or anti-neoplastic agents within 3 months before baseline. 13. Known history of hypothalamic-pituitary-adrenal axis impairment or any other disturbance of the adrenal function (e.g. Cushing or Addison disease). 14. Known or suspected severe renal insufficiency or severe hepatic disorders or severe heart disease. 15. Patients who have a history of or current diagnosis of glaucoma or posterior subcapsular cataracts or any other ocular condition that, in the opinion of the Investigator, would place study patient at undue risk. 16. 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. 17. 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. 18. Use within 4 weeks before baseline of 1) oral or intravenous corticosteroids, 2) UVA/UVB therapy, 3) PUVA (psoralen plus ultraviolet A therapy, 4) topical tacrolimus, 5) topical pimecrolimus, 6) systemic retinoids or 7) any other systemic psoriasis treatment 19. Use of tanning booths or nonprescription UV light source within 2 weeks before baseline. 20. Use within 8 weeks before baseline of 1) immunomodulators or immunosuppressive therapies or 2) interferon. 21. Use within 14 days before baseline of calcipotriene or other Vitamin D preparations. 22. 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. 23. Use of systemic antibiotics or prescription-strength systemic anti-inflammatory agents within 1 month before baseline. 24. Use of the following within 2 weeks before baseline: a. Topical anti-psoriatic agents. b. Topical corticosteroids. c. Topical retinoids. d. Topical anti-inflammatory agents. e. Medicated shampoos for scalp psoriasis (including coal tar shampoo). f. New regimens of beta blockers. g. Lithium preparations.

	h. Anti-malarial agents. 25. Patient has been treated within 12 weeks before baseline with any biological therapies for psoriasis. 26. Inability to understand the protocol requirements, instructions, and study-related restrictions, the nature, scope, and possible consequences of the clinical study. 27. 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. 28. Receipt of any drug as part of a research study within 30 days before baseline. 29. The patient is a member of the investigational study staff or a member of the family of the investigational study staff. 30. Previous participation in this study.
Criteria for Evaluation	**Primary Outcome Measures:** Hypothalamic Pituitary Adrenal (HPA) Axis Response to Cosyntropin demonstrating the absence or presence of adrenal suppression at the end of treatment defined by the following criteria: 30 minute post Cortrosyn™ injection level cortisol level of ≤ 18 mcg/100ml during the Cortisol Response Test **Secondary Outcome Measures:** Hypothalamic Pituitary Adrenal (HPA) Axis Response to Cosyntropin demonstrating the presence of adrenal suppression at the end of treatment with % Scalp Affected as a covariate
HPA Axis Evaluation	If at the end of the study the patient has a cortisol response test that is suggestive of HPA axis suppression, they will have a follow up test at least every 4 weeks in accordance to the follow up calendar in Appendix D or until such time as the Investigator considers the adrenal function has turned to normal. Patients with normal adrenal function at baseline will be included in the HPA Axis evaluation. **Primary Analysis:** Proportion of patients in the study with HPA axis suppression following treatment with the study medication. **Secondary Analysis:** A logistic regression of the proportion of patients in the study with HPA axis suppression will be performed with % scalp affected as a covariate.

Safety Parameters	Adverse events will be classified using standard MedDRA terminology Version 19 or higher and summarized over all patients. Adverse events reported during the study will be tabulated in summary table by type, date of onset, date of resolution, incidence, severity, action taken, outcome and Investigator's opinion of relationship to the study product. 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. Concomitant medication use during the study will be tabulated by patient. Ocular safety evaluations will be assess 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. Ocular discomfort will be assessed by the patients and reported to staff during clinic visits.
Sample Size Determination	The sample size of 5-10 evaluable patients was deemed appropriate to meet the objectives of the study.

5.0 STUDY SCHEMATIC

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
Day	**1**	**14 ± 2**	**29 ± 2**	**42 ± 4**
Procedures	Screening/ Enrollment **Before 12 pm**	Interim Visit	End of Study/Early Termination **Before 12 pm**	Telephone Follow-Up Visit
Informed Consent/Assent	X			
Medical History and Demographics	X			
Vital Signs	X	X	X	
Pregnancy Test*	X	X	X	
Physical Exam	X		X	
HEENT Exam	X	X	X	
% Scalp Affected	X	X	X	
Investigator Global Assessment	X	X	X	
Concomitant Medication	X	X	X	X
Laboratory Evaluations	X		X	
Cortisol Response Test	X		X	
Confirm Inc/Exc Criteria	X			
Dispense Wristband	X			
Weigh and Dispense Study Product	X	X		
Collect and Weigh Study Product		X	X	
Dispense/Review Patient Diary	X	X	X	
Ocular Assessment		X	X	
Adverse Events		X	X	X
Evaluation of Patient Compliance to the Protocol		X	X	

* Pregnancy test will be carried out for females of childbearing potential.

6.0 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Term
ADL	Activities for Daily Living
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
HR	Heart Rate
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
mITT	Modified Intent-to-Treat
NDA	New Drug Application
NSAID	Non-Steroidal Anti-Inflammatory Drug
OHRP	Office of Human Rights Protection
OTC	Over-the-Counter
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 patients with moderate to severe psoriasis.

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]

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]

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 (Tazorac®, 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.[1,2,5-7]

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) 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.[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.[1,2,5-7]

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 0.25% shampoo) 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

In some instances high potency steroids applied topically have been known to cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis. In order to assess HPA axis function plasma levels of cortisol are measured before (basal) and after a bolus administration of synthetic α 1-24-adrenocorticotropic hormone (ACTH). In this study Cortrosyn™ (cosyntropin, a synthetic subunit of ACTH) (Amphstar Pharmaceuticals, Inc.) will be used according to manufacturer instructions to assess HPA axis function (See Appendices D, E).[9] Recovery from steroid-induced adrenal insufficiency is usually rapid after the treatment is withdrawn.[10] See Appendix D for further explanation of the evaluation of the role of topical corticosteroids in HPA axis suppression.

Taro Pharmaceuticals U.S.A. has recently completed an open label safety and efficacy study to assess adrenal suppression in adults with moderate to severe plaque psoriasis after 4 weeks of treatment under maximal use conditions with the test product, desoximetasone 0.25% spray. Of 21 evaluable subjects, adrenal suppression was identified in 1 of 12 subjects having involvement of 10-15% of body surface area (BSA) and 2 of 9 subjects having involvement of > 15% of BSA after treatment with Topicort® Topical Spray twice a day for 28 days. Adrenal function returned to normal at the first follow-up visit, which was 28 days after the end of treatment, for all 3 of these patients[11]

This study design is based on similar studies performed, submitted and accepted by the FDA for recently approved high potency spray and foam topical corticosteroid formulations, topical corticosteroid/topical vitamin D3 analogue combination agents, and recommendations from the FDA in IND 101789 Guidance Meeting that took place on 01/14/2015 and an FDA Advice Letter dated 04/27/2015 (Reference ID: 3740601) for desoximetasone 0.15% topical spray, and recommendations provided by the FDA in the Meeting Request – Written Reponses Letter dated 09/18/2013 for PIND 118881 (Reference ID 3374240) for desoximetasone 0.25% shampoo.[9,12-15]

7.4 Risks and Benefits

Known adverse reactions to topical corticosteroids include burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae and milliaria. Dosing for extended periods of time may result in suppression of adrenal function.

Cortrosyn™ for injection is intended diagnostic and not therapeutic use and adverse reactions other than a rare hypersensitivity reaction are not anticipated. Known reactions are slight whealing with erythema at the site of injection.

The subject may benefit from clearing of the lesions and improvement of the condition of the disease. If the drug is approved, then many patients may benefit from its use.

The potential risks and benefits of participation in the study will be explained to the patient verbally and written in the informed consent form.

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 as compensation for time and inconvenience related to study participation including costs associated with travel to and from the medical facility.

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

8.0 STUDY OBJECTIVES

The objectives of this study are to:

1. Evaluate the potential of desoximetasone 0.25% shampoo to suppress HPA axis function in patients with moderate to severe scalp psoriasis.
2. Evaluate the efficacy parameters and adverse event (AE) profiles of desoximetasone 0.25% shampoo administered to patients with moderate to severe scalp psoriasis.

9.0 INVESTIGATIONAL PLAN

9.1 Study Design and Plan Description

This open-label, safety study is designed to evaluate the potential for adrenal suppression after maximal use treatment with desoximetasone 0.25% shampoo (Taro Pharmaceuticals, U.S.A.), for the treatment of moderate to severe scalp psoriasis.

Up to 5-10 eligible patients with stable plaque psoriasis of the scalp that satisfy all eligibility criteria will be enrolled into the study at Visit 1. Patients must be overall in good health. They should have a current diagnosis of moderate to severe scalp psoriasis with IGA score of at least 3 or 4.

Up to 5-10 patients with a confirmed diagnosis of moderate to severe scalp psoriasis

Patients enrolled in the study will apply product once daily for 28 days, according to provided instructions. Each patient is expected to receive 28 doses of study product.

Patients will attend a total of 3 Clinic Visits and a telephone follow-up phone call (Visit 4) as follows:

- **Visit 1 (Day 1)**: Enrollment
- **Visit 2 (Day 14±2)**: Interim Visit
- **Visit 3 (Day 29 ± 2)**: End of Study or Early Termination
- **Visit 4 (Day 42± 4)**: Follow-up Telephone Phone Call

The primary endpoint is the proportion of patients in the study with HPA axis suppression following treatment with the study medication.

The safety profile of each treatment group will be evaluated by comparing adverse events.

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 study design is based on similar studies performed, submitted and accepted by the FDA for recently approved high potency spray and foam topical corticosteroid formulations, topical corticosteroid/topical vitamin D3 analogue combination agents, and recommendations from the FDA in IND 101789 Guidance Meeting that took place on 01/14/2015 and an FDA Advice Letter dated 04/27/2015 (Reference ID: 3740601) for desoximetasone 0.15% topical spray, and recommendations provided by the FDA in the Meeting Request – Written Reponses Letter dated 09/18/2013 for PIND 118881 (Reference ID 3374240) for desoximetasone 0.25% shampoo.[9,12-15]

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Male or non-pregnant, non-lactating females 12-17 years of age.
2. If female and of childbearing potential, prepared to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g., condom, IUD, oral, transdermal or injected hormonal contraceptives). Female patients using hormonal contraceptives should have been on the same product/dosing regimen for at least 28 days before baseline and should not change this regimen during the study.
3. Signed IRB approved informed consent given by parent(s) or legally acceptable guardian(s) following their receipt of verbal and written information about the study. For patients age 12-17 years of age 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.
4. Patients with a confirmed clinical diagnosis of stable plaque psoriasis of the scalp with ≥ 20% scalp affected.
5. Investigator Global Assessment (IGA) score of 3 (Moderate) or 4(Severe)

9.3.2 Exclusion Criteria

1. Females who are 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.
2. Patients < 12 years of age or > 17 years of age.
3. Patients whose scalp psoriasis necessitates systemic or other concomitant topical therapies during the study. Concomitant treatment of body psoriasis with OTC topical products, including emollients, is allowed.
4. IGA score < 3.
5. Scalp psoriasis with < 20% scalp affected.
6. History of psoriasis that has been unresponsive to topical corticosteroid therapy.
7. 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).

8. History of an adverse reaction to Cortrosyn™ or similar test reagents
9. 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.
10. 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.
11. Patient has a significant history or current evidence of chronic infectious disease, system disorder, organ disorder or insufficiency, immunosuppression (from medical treatment or disease), organ transplant or other medical condition that, in the Investigator's opinion, would place the study patient at undue risk by participation in the study.
12. Patient is currently receiving or has received any radiation therapy or anti-neoplastic agents within 3 months before baseline.
13. Known history of hypothalamic-pituitary-adrenal axis impairment or any other disturbance of the adrenal function (e.g. Cushing or Addison disease).
14. Known or suspected severe renal insufficiency or severe hepatic disorders or severe heart disease.
15. Patients who have a history of or current diagnosis of glaucoma or posterior subcapsular cataracts or any other ocular condition that, in the opinion of the Investigator, would place study patient at undue risk.
16. 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.
17. 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.
18. Use within 4 weeks before baseline of 1) oral or intravenous corticosteroids, 2) UVA/UVB therapy, 3) PUVA (psoralen plus ultraviolet A therapy, 4) topical tacrolimus, 5) topical pimecrolimus, 6) systemic retinoids or 7) any other systemic psoriasis treatment
19. Use of tanning booths or nonprescription UV light source within 2 weeks before baseline.
20. Use within 8 weeks before baseline of 1) immunomodulators or immunosuppressive therapies or 2) interferon.
21. Use within 14 days before baseline of calcipotriene or other Vitamin D preparations.
22. 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.
23. Use of systemic antibiotics or prescription-strength systemic anti-inflammatory agents within 1 month before baseline.
24. Use of the following within 2 weeks before baseline:
    a. Topical anti-psoriatic agents.

b. Topical corticosteroids.

c. Topical retinoids.

d. Topical anti-inflammatory agents.

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

f. New regimens of beta blockers.

g. Lithium preparations.

h. Anti-malarial agents.

25. Patient has been treated within 12 weeks before baseline with any biological therapies for psoriasis.
26. Inability to understand the protocol requirements, instructions, and study-related restrictions, the nature, scope, and possible consequences of the clinical study.
27. 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.
28. Receipt of any drug as part of a research study within 30 days before baseline.
29. The patient is a member of the investigational study staff or a member of the family of the investigational study staff.
30. 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:

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), Tazorec ® (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.	12 weeks
Chemotherapy Radiation therapy		3 months
Systemic corticosteroids Systemic antipsoriatic treatment Systemic antibiotics PUVA therapy UVB therapy Prescription strength systemic anti-inflammatory agents	Prednisone (Short and occasional use of intranasal, inhaled or ophthalmic corticosteroids for acute and transitory conditions [e.g. allergic rhinitis] up to 1 mg per day is acceptable) methotrexate, cyclosporine, hydroxyurea *the use of acetylsalicylic acid for prophylactic use up to 325 mg/day is allowed, provided that the patient is on a stable dose for at least 3 months and the regimen will remain constant throughout the study	4 weeks
Systemic retinoids	Soriatane® (acitretin), Isotretinoin etc	4 weeks
Systemic immunosuppressive drugs	tacrolimus, pimecrolimus	8 weeks

Patients and 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.

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 to continue using the same brand/type and frequency of use throughout the study.

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 should 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.

All patients who administer at least one dose of randomized study medication will be included in the safety analysis. If a patient terminates from the study early, all efforts will be made to complete their next visit study procedures. In case of early termination the Investigator shall fully document the reason for early termination. Reasons for early termination may include the following:

- Patient withdrew consent
- Significant adverse event that led the Investigator or patient to withdraw for safety reasons
- 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 the evaluation of the patient's clinical state to an extent considered significant by the Investigator
- Signs and symptoms of possible HPA axis suppression
- Protocol deviations/violations that in the Investigator's opinion warrant discontinuation

Non-compliance with dosing need not be a reason for early termination. Patients who withdraw or are removed from the study will not be replaced. In the event a patient withdraws or is dropped from the study for any reason, the Investigator will request return of the unused product and report the reason for the discontinued participation.

When a patient discontinues early from the study, all study procedures required for the end of study should be performed at their last study visit. Patients who are discontinued from the study will be evaluated for safety and will be given, or referred for, appropriate treatment.

9.4 Treatments

9.4.1 Treatments Administration

The patient will be instructed to apply the study product to psoriasis-affected areas of the dry scalp once daily for 28 days. 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.

The patient will be instructed to apply the medication once daily until the patient's next scheduled visit. 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.

At Visit 1 qualified study patients will be provided with one 120 ml bottle of desoximetasone 0.25% shampoo along with instructions for dosing. This bottle should be weighed before dispensing and the weight recorded. At Visit 2, the bottle should be collected and weighed and a new 120 ml bottle of shampoo should be weighed and dispensed along with dosing instructions. This bottle will be returned and weighed at Visit 3.

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.

9.4.2 Identity of Investigational Product

Desoximetasone 0.25% shampoo, w/w will be used in this study

9.4.3 Method of Assigning Patients to Treatment Groups

Patients will be assigned to the treatment in an open label fashion.

9.4.4 Packaging

This is an open-label study. The study product will contain a label with the following information:

- Protocol number
- Bottle number
- Space for patient number, patient's initials and dispensed date
- A note that the drug is for Investigational Use Only

9.4.5 Accountability

The Investigator or designee will maintain an inventory of all study product supplies received.

9.5 Study Conduct

The cortisol response test is to be done in the morning as the body's peak cortisol level is directly related to the event of awakening. Visit 1 and Visit 3 should be scheduled before noon and subjects should not apply the study drug within 12 hours of Visit 3.

9.5.1 Visit 1: Screening/Enrollment (Day 1), before 12 pm

1. **Informed Consent/Assent**: Patients who are willing to comply with study procedures will read and sign the assent form. 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.
2. **Medical History and Demographics**: Review the patient's demographic and medical history including concomitant medication use within the last 12 weeks.
3. **Physical Examination**: A general physical exam will be conducted.
4. **HEENT Examination**: A general exam of the head, eyes, ears, nose and throat will be conducted at the clinic.

5. **% 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 B.
6. **Vital Signs**: The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
7. **Pregnancy Test**: A pregnancy test will be required of all females of child bearing potential prior to enrollment.
8. **Investigator's Global Assessment**: Patient's scalp will be examined to determine a psoriasis severity score based on a global assessment of plaque elevation, scaling and erythema by the Investigator/designated clinician (refer to Appendix A). Patients with a score of 3 or more, indicating moderate to severe psoriasis will be included in the study.
9. **Concomitant Medication**: Review with the patient use of concomitant medication within the last 12 weeks.
10. **Confirm Inclusion/Exclusion Met**: Confirm the patient meets all inclusion/exclusion criteria.
11. **Laboratory Evaluations**: A blood sample will be collected for hematology and clinical chemistry testing. (See Appendix F).
12. **Cortisol Response Test**: All patients will have a cortisol response test performed according to the procedure detailed in Appendix D.
13. **Dispense Study Product:** If patient is eligible to enroll, record the weight of one bottle of study product and dispense with instructions.
14. **Provide Dosing Diary:** Provide diary and instruct patient regarding how it is to be filled out and how study product is to be used.
15. **Provide Patient Wristband:** Each patient will receive a wristband to indicate that the patient is using a medication that has the potential to cause HPA axis suppression.
16. Schedule Visit 2.

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

1. **Pregnancy Test**: A pregnancy test will be required of all females of childbearing potential.
2. **Vital Signs**: The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
3. **HEENT Examination**: A general exam of the head, eyes, ears, nose and throat will be conducted at the clinic
4. **% 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 B
5. **Investigator's Global Assessment**: Patient's scalp will be examined to determine a psoriasis severity score based on a global assessment of plaque elevation, scaling and erythema by the Investigator/designated clinician (refer to Appendix A).

6. **Concomitant Medication:** Review with the patient use of new or change in ongoing concomitant medication since Visit 1.
7. **Adverse Events:** Patients will be questioned about any health status changes/adverse events since last visit. All events will be recorded.
8. **Ocular Assessments**: Patients will be questioned about any ocular discomfort as a part of safety assessments (refer to Appendix C)
9. **Evaluation of Patient Compliance to the Protocol**: Collect and review patient's dosing diary for compliance and provide a new diary. Non-compliance with dosing does not warrant dismissal from the study. Counsel non-compliant patients on dosing requirements of the study.
10. **Collect Study Product**: The used bottle of study drug will be collected and the weight recorded.
11. **Dispense New Study Product**: If patient continues in the study, record weight of one new bottle of study product and dispense.
12. **Provide Dosing Diary**: If patient continues in the study, provide a new dosing diary.
13. Schedule Visit 3

9.5.3 Visit 3 (Day 29 ± 2): End of Study or Early Termination, Before 12 pm

1. **Vital Signs**: The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
2. **Pregnancy Test:** A pregnancy test will be required of all females of child bearing potential.
3. **Physical Exam**: A general physical exam will be conducted.
4. **HEENT Examination**: A general exam of the head, eyes, ears, nose and throat will be conducted at the clinic
5. **% 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 B
6. **Investigator's Global Assessment**: Patient's scalp will be examined to determine a psoriasis severity score based on a global assessment of plaque elevation, scaling and erythema by the Investigator/designated clinician (refer to Appendix A).
7. **Concomitant Medication**: Review with the patient use of new or change in ongoing concomitant medication since Visit 2.
8. **Adverse Events**: Patients will be questioned about any health status changes/adverse events since last visit. All events will be recorded.
9. **Ocular Assessments**: Patients will be questioned about any ocular discomfort as a part of safety assessments (refer to Appendix C)
10. **Evaluation of Patient Compliance to the Protocol**: Collect and review patient's dosing diary for compliance.

11. **Collect Study Product**: The used bottle of study product will be collected and the weight recorded.
12. **Laboratory Evaluations**: A blood sample will be collected for hematology and clinical chemistry testing. (See Appendix F).
13. **Cortisol Response Test**: All patients will have a cortisol response test performed according to the procedure detailed in Appendix D.

9.5.4 Visit 4 (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 or new or changed concomitant medications that may have occurred.

9.6 Study Procedures

9.6.1 Informed Consent/Assent

At Visit 1, before any study related procedures, the parent/legal guardian must sign the IRB-approved consent form. 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 assent form and parent/legal guardians signing an informed consent form. If any other language is required, translation will be performed by a certified translator.

9.6.2 Demographics

At screening, 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 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 12 weeks.

9.6.4 Vital Signs

The patient's vital signs will be recorded (heart rate, blood pressure, temperature and respiration rate) at Visit 1, 2, and 3.

9.6.5 Physical Exam

A general physical exam will be conducted at Visit 1 and Visit 3. The physical exam must include a dermatological examination as a minimum.

9.6.6 HEENT Exam

A head, eye, ear, nose, throat (HEENT) examinations will be conducted at each clinic visit (Visit 1, 2 and 3).

9.6.7 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 B.[16]

9.6.8 Investigator Global Assessment

Patient will be examined to determine the severity of scalp psoriasis based on a global assessment of plaque elevation, scaling and erythema by the Investigator/designated clinician (refer to Appendix A).

9.6.9 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.

9.6.10 Concomitant Medication Use

At Visits 1-3 and during the follow-up phone call (Visit 4) patients will be questioned about current and concomitant medication use over the previous 12 weeks. At all Interim Visits patients will be questioned about ongoing or new concomitant medication use.

9.6.11 Pregnancy Test

Urine pregnancy tests on females of childbearing potential will be performed at Visit 1, 2, and 3. The test must be negative for the patient to be eligible for inclusion in the study. If the patient is of non-childbearing potential, 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 completed. The outcome of the pregnancy will be followed by the Investigator to birth or early termination as appropriate. The pregnancy will be reported as an AE.

9.6.12 Dispensing Study Product

At Visit 1 patients that satisfy all of the inclusion/exclusion criteria will be dispensed one bottle of the study product and dosing instructions. At Visit 2 (Day 14) a new bottle of study product will be dispensed.

The weight of the study product should be recorded before dispensing.

9.6.13 Collecting Study Product

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

9.6.14 Dosing Instructions and Diary

Patients will be provided with a diary to record the time and date of dosing, other concomitant medications and adverse events. Patients applying fewer than 75% or more than 125% of the required doses will be considered non-compliant with dosing. Compliance with dosing will be verified by the use of the patient diaries.

9.6.15 Dosing Compliance

Dosing compliance will be checked by site staff at Visits 2 and 3. Patients taking fewer than 75% or more than 125% of the scheduled doses will be considered non-compliant with dosing. Compliance with dosing will be verified by the use of the patient diaries.

		Compliance Criteria	
Duration	Scheduled Doses	Not more than 125% (doses)	Not less than 75% (doses)
28 Days	28	35	21

9.6.16 Patient Wristband

Each patient who enters the study will be provided with a wristband at Visit 1 to identify that the patient is taking a medication that could potentially cause HPA axis suppression. The patient should be instructed to wear the wristband for the duration of the study.

9.6.17 Laboratory Evaluation

At Visit 1 and Visit 3 a blood sample will be collected for hematology and clinical chemistry testing (See Appendix F).

9.6.18 Cortisol Response Test

At Visit 1 and Visit 3 all patients will have a cortisol response test performed according to the procedure detailed in Appendix D. The resulting blood sample should be sent to ACM Global Laboratory for immediate testing.

The test at the End of Study visit should not be performed if the patient dosed within 12 hours.

A patient will be considered to have normal basal cortisol level and adrenal function if they meet all three criteria listed below under Normal. Failure to meet any of these criteria is indicative of abnormal adrenal function or potential HPA axis suppression, even in absence of related symptoms (e.g. nausea, headache, myalgia, fatigue or loose stool); for abnormal results, the patient will be monitored in accordance to the follow-up schedule below.

	Cortisol Results	
	Normal	Abnormal
Basal (pre Cortrosyn™ injection)	≥ 5 mcg/100ml	< 5 mcg/100ml
30 minutes post	≥ basal value + 7	< basal value + 7

Cortrosyn™ injection	> 18 mcg/100ml	≤ 18 mcg/100ml

HPA Axis suppression will be defined as a 30 minute post Cortrosyn™ injection level cortisol level of ≤ 18 mcg/100ml. If the Visit 1 Cortisol Response Test shows signs of HPA axis suppression as defined above the patient will be contacted and instructed to discontinue the use of study product, not to initiate any new steroid therapy, topical or otherwise and an End of Study Visit will be scheduled to conduct a Cortisol Response Test at least 28 days after the initial Cortisol Response Test at Visit 1 to assess for HPA axis suppression. At Visit 3 the study treatment period will be over, any patients with results of HPA axis suppression will be advised not to initiate any new steroid therapy, topical or otherwise, and to return to the site in 28 days at which time they will be assessed for HPA axis suppression.

Any patient presenting with symptoms of HPA axis suppression, such as nausea, headache, myalgia, fatigue or loose stool, will be referred to an endocrinologist. As an additional safety precaution, wristbands identifying the patient as someone suffering from adrenal suppression secondary to steroid withdrawal will be provided to alert medical personnel should any emergencies arise before adrenal function returns to normal.

If the results of the cortisol response test still show signs of HPA axis suppression 28 days after discontinuing therapy the patient will be asked to return in 28 days (56 days after discontinuing steroid therapy) for another follow-up test. If the patient is still showing signs of HPA axis suppression 56 days after discontinuing steroid therapy and presents with related symptoms, the patient will be referred to an endocrinologist.

If HPA axis suppression persists for 56 days after discontinuing steroid therapy, but the patient has no symptoms they will be asked to return in 28 days (84 days after discontinuing steroid therapy) for another follow-up test. If HPA axis suppression persists for 84 days after discontinuing steroid therapy the patient will be referred to an endocrinologist regardless of symptoms.

Patients should not be subjected to Cortrosyn™ testing, or any other challenge to their adrenal response, any sooner than 4 weeks from their last Cortrosyn™ test.

Follow-Up Schedule for Patients showing signs of HPA Axis Suppression

Days after d/c	HPA Results	Symptoms	Patient Course
28	Normal	N/A	Study over
28	Abnormal	Yes	Refer to endocrinologist
28	Abnormal	No	Repeat test in 28 days
56	Normal	N/A	Study over
56	Abnormal	Yes	Refer to endocrinologist
56	Abnormal	No	Repeat test in 28 days
84	Normal	N/A	Study over
84	Abnormal	Yes or No	Refer to an endocrinologist

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 19 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 that 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 Fanzio, MD
Medical Monitor
Phone 412-363-3300 x 597
Fax 412-291-3171

Novum will report any Serious Adverse Event to Taro.

Documentation of serious or unexpected adverse events and follow-up information should be sent to Taro's SAE Coordinator and Taro's Drug Safety Manager within 24 hours from Novum being made aware of the SAE. Following is the contact information:

Taro SAE Coordinator:	Taro Drug Safety Manager:
Danielle Simpson Coordinator, Clinical Operation Taro Pharmaceuticals USA Inc. Tel: 914-345-9001 ext.6234 Email: danielle.simpson@taro.com	Margo Wyatt, RN, BSN, Associate Director, Drug Safety Taro Pharmaceuticals U.S.A., Inc. Tel: 914-345-9001 Ext. 6758 Email: margo.wyatt@taro.com **and** taropvus@taro.com

The Sponsor must notify FDA of a fatal or life-threatening adverse event as soon as possible but no later than 7 calendar days from reporting the event by the Investigator. 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.

10.1.1 Determination of Sample Size

The sample size of 5-10 evaluable patients was deemed appropriate to meet the objective of the study

10.1.2 Safety Analysis of Potential HPA Axis Suppression

Dosing will be once daily for 28 days. Patients with normal adrenal function at baseline, use at least 21 doses of the study product and have data from a post-treatment cortisol response test will be included in the analysis. Patients who have not used 21 doses of the study product will be excluded from the primary analysis of HPA axis suppression.

The primary analysis of interest is to assess the proportion of patients considered to have demonstrated possible HPA axis suppression following treatment with the study medication. As a secondary analysis of the data a logistic regression of the proportion of patients in the study with HPA axis suppression will be performed with % scalp affected as a covariate. See Appendix D for results from the cortisol response test considered indicative of potential HPA axis suppression.

For all patients the actual amount of desoximetasone (mg) applied during the study will be calculated from recorded bottle weights and presented.

After the completion of 5 patients an interim analysis will be performed and presented.

10.2 Safety Analysis

Safety analysis will be conducted on all patients who applied at least one dose of study product.

Adverse events will be classified using standard MedDRA terminology Version 19 or higher and summarized over all patients. Adverse events reported during the study will be tabulated in summary table listing by type, date of onset, date of resolution, incidence, severity, action taken, outcome and Investigator's opinion of relationship to the study product will be prepared. 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.

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

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. Ocular discomfort will be assessed by patients and reported to staff during clinic visits (Appendix C).

Adverse medical events experienced by the patients will be tabulated. The relationship of AEs, if any, to the study product will be assessed by the Investigator. Adverse events assessed as definite, probable, possible or not related to the study drug will be presented. Shift analysis using the categories, below, above and within the laboratory normal range will be performed to identify any specific laboratory parameter that shows a trend toward potentially clinically significant changes.

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 64th World Medical Association General Assembly, October 2013.[17-20]

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 end of study (Visit 3) 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 drug will be returned to Novum.

11.2.6 Drug Storage

All study product 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 product receipt, dispensing, and return. At the end of the study, all study product will be returned to Novum.

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 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., Norplant®), Depo-Provera®, double barrier methods (e.g., condom and spermicide) or IUD. Prior to 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, prior to study participation. Pregnancy testing will be performed at Visits 1, 2 and 3 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 Investigational Product exposure, the Investigational 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 to the contacts listed in section 9.8.2.

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.

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 in e-CTD format will be prepared that 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.

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. *The Journal of clinical and aesthetic dermatology* **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 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).
7 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. *The British journal of dermatology* **168**, 954-967, doi:10.1111/bjd.12276 (2013).
8 Taro Pharmaceuticals. Package Insert for TOPICORT® (desoximetasone) Topical Spray, 0.25%. (2013).
9 FDA. Summary Basis of Approval - Luxiq (Betamethasone Valerate) Foam (NDA 20-934) - Connetics Corporation (1999).
10 Hengge, U. R., Ruzicka, T., Schwartz, R. A. & Cork, M. J. Adverse effects of topical glucocorticosteroids. *Journal of the American Academy of Dermatology* **54**, 1-15; quiz 16-18, doi:10.1016/j.jaad.2005.01.010 (2006).
11 Product Label for TOPICORT®(desoximetasone) Topical Spray, 0.25%. (April 2013).
12 Product Label for Cortrosyn™ Amphastar Pharmaceuticals, Inc. **August** (2009).
13 Summary Basis of Approval OLUX® Clobetasol 0.05% Foam. NDA#021-142. Connetics. **May** (2000).
14 Deparment of Health and Human Services, F. (January 14, 2015).
15 Department of Health and Human Services, F. FDA Correspondence Advice Letter. IND 101789. (April 27, 2015).
16 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).
17 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).
18 FDA. 21CFR Part 50 Protection of Human Subjects. *Department of Health and Human Services, Subchapter A-General* **1** (2014).
19 FDA. 21CFR Part 56 Institutional Review Boards. *Department of Health and Human Services, Subchapter A-General* **1** (2014).
20 FDA. 21CFR 312.32: IND Safety Reporting. (2010).

13.0 APPENDICES

13.1 APPENDIX A

Investigator Global Assessment (IGA)

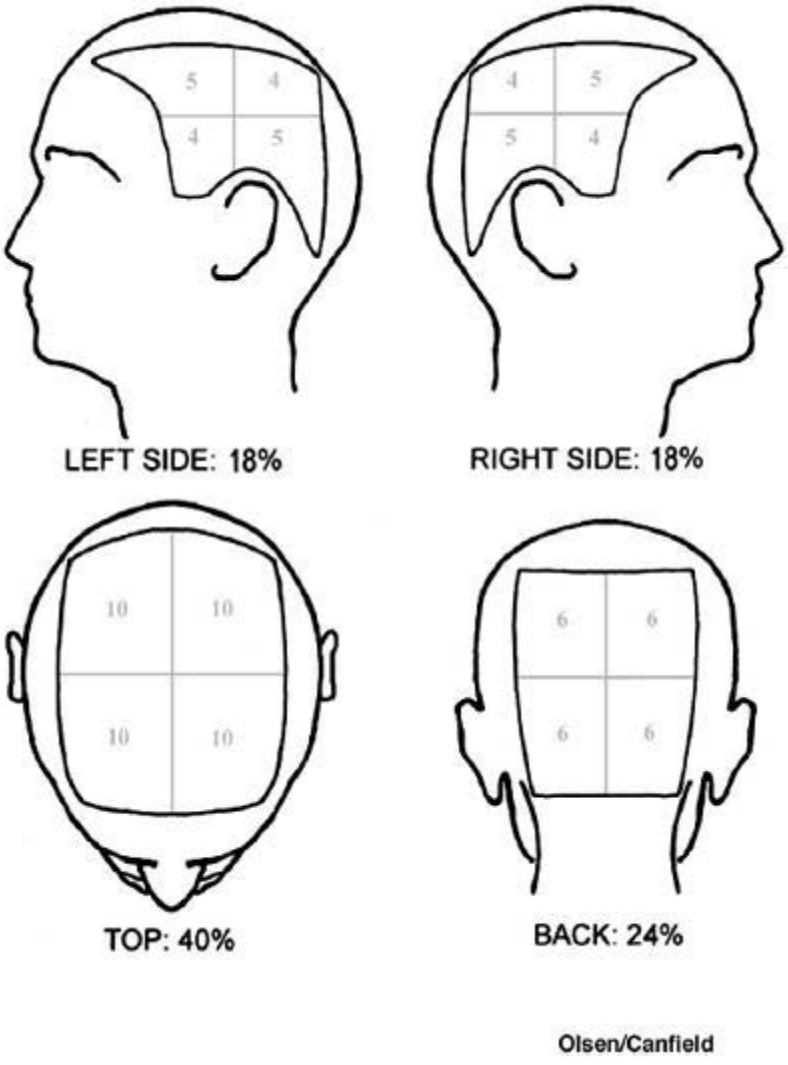
To be eligible for inclusion in the study the IGA must be 3 or 4 at baseline. Patients will be considered to have shown improvement in disease severity if the IGA score decreases by at least one unit from the baseline score, and will be considered a treatment success if the IGA score decreases at least 2 units from the baseline score.

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

Percent Scalp Affected

Investigators will use the following chart to identify areas and estimate scalp surface area affected by psoriasis plaques.[16]



13.3 APPENDIX C

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.

13.4 APPENDIX D

Cortisol Response Test

This cortisol release test is modified from the procedure of Wood et al as described in the Product Label for Cortrosyn™ (cosyntropin) for injection (Amphstar Pharmaceuticals, Inc.).

The procedure is as follows:

1. A single 5 ml blood sample should be taken as the basal sample.
2. 0.25 mg (a single vial) of Cortrosyn™ (cosyntropin) should be reconstituted with 1.0ml of 0.9% sodium chloride injection USP injected intramuscularly. In patients under 3 years of age, 0.125mg of Cortrosyn™ will be used.
3. 30 minutes after the IM injection a second 5 ml blood sample should be obtained. The resulting two serum samples (at least 1 ml of serum in each) should be processed and labeled according to the instructions provided and sent the same day to ACM Global Laboratory for analysis of basal and post stimulated serum cortisol concentration.

The resulting blood samples should be sent to ACM Global Laboratory for immediate testing.

The test at the End of Study visit should not be performed if the patient dosed within 12 hours.

A patient will be considered to have normal basal cortisol level and adrenal function if they meet all three criteria listed below under Normal. Failure to meet any of these criteria is indicative of abnormal adrenal function or potential HPA axis suppression.

	Cortisol Results	
	Normal	Abnormal
Basal (pre Cortrosyn™ injection)	≥ 5 mcg/100ml	< 5 mcg/100ml
30 minutes post Cortrosyn™ injection	≥ basal value + 7	< basal value + 7
	> 18 mcg/100ml	≤ 18 mcg/100ml

HPA Axis suppression will be defined as a 30 minute post Cortrosyn™ injection level cortisol level of ≤ 18 mcg/100ml. If the Visit 1 Cortisol Response Test shows signs of HPA axis suppression as defined above the patient will be contacted and instructed to discontinue the use of study product, not to initiate any new steroid therapy, topical or otherwise and an End of Study Visit will be scheduled to conduct a Cortisol Response Test at least 28 days after the initial Cortisol Response Test at Visit 1 to assess for HPA axis suppression. At Visit 3 the study treatment period will be over, any patients with results of HPA axis suppression will be advised not to initiate any new steroid therapy, topical or otherwise, and to return to the site in 28 days at which time they will be assessed for HPA axis suppression.

Any patient presenting with symptoms of HPA axis suppression, such as nausea, headache, myalgia, fatigue or loose stool, will be referred to an endocrinologist. As an additional safety precaution, wristbands identifying the patient as someone suffering from adrenal suppression secondary to steroid withdrawal will be provided to alert medical personnel should any emergencies arise before adrenal function returns to normal.

If the results of the cortisol response test still show signs of HPA axis suppression 28 days after discontinuing therapy they will be asked to return in 28 days (56 days after discontinuing steroid therapy) for another follow-up test. If the patient is still showing signs of HPA axis suppression 56 days after discontinuing steroid therapy and presents with related symptoms they will be referred to an endocrinologist.

If HPA axis suppression persists for 56 days after discontinuing steroid therapy, but the patient has no symptoms they will be asked to return in 28 days (84 days after discontinuing steroid therapy) for another follow-up test. If HPA axis suppression persists for 84 days after discontinuing steroid therapy patients will be referred to an endocrinologist regardless of symptoms.

Patients should not be subjected to Cortrosyn™ testing, or any other challenge to their adrenal response, any sooner than 4 weeks from their last Cortrosyn™ test.

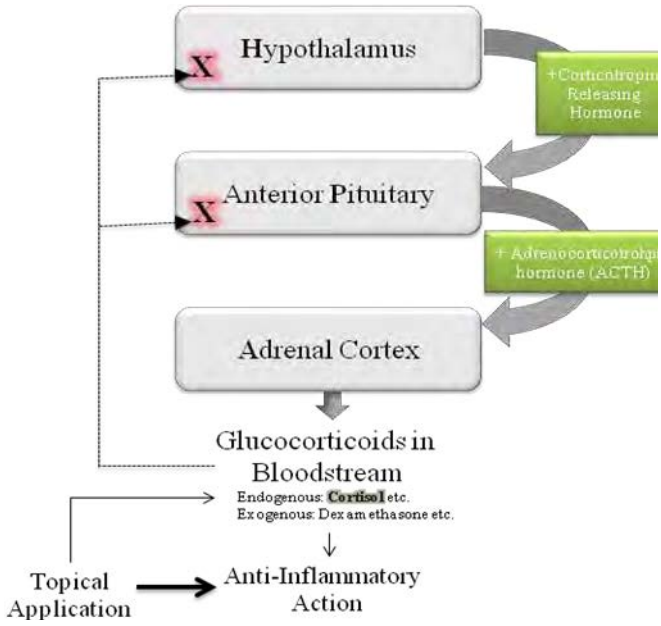
Follow-Up Schedule for Patients showing signs of HPA Axis Suppression

Days after d/c	HPA Results	Symptoms	Patient Course
28	Normal	N/A	Study over
28	Abnormal	Yes	Refer to endocrinologist
28	Abnormal	No	Repeat test in 28 days
56	Normal	N/A	Study over
56	Abnormal	Yes	Refer to endocrinologist
56	Abnormal	No	Repeat test in 28 days
84	Normal	N/A	Study over
84	Abnormal	Yes or No	Refer to an endocrinologist

13.5 APPENDIX E

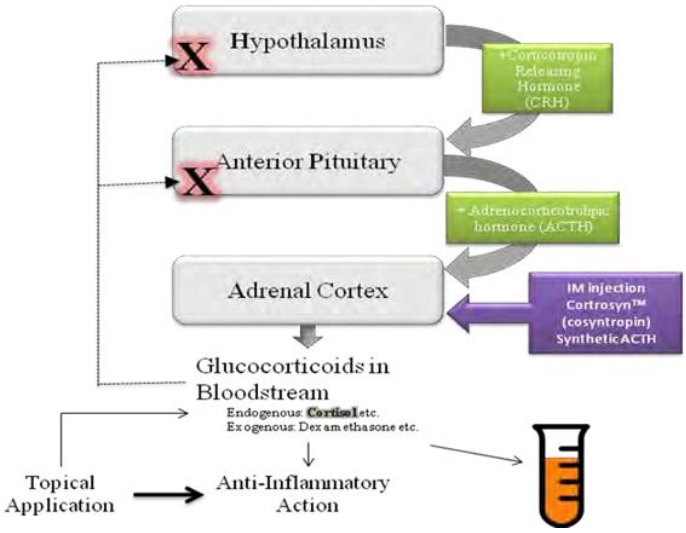
Evaluation of HPA Axis Suppression

Corticosteroid Effect on HPA Axis Feedback Loop



The Hypothalamus secretes Corticotrophin Releasing Hormone (CRH) which triggers the anterior pituitary to release Adrenocorticotrophin Hormone (ACTH). ACTH stimulates the adrenal cortex to release glucocorticosteroids into the bloodstream. Increased levels of circulating glucocorticoids in the bloodstream send a signal to the hypothalamus to decrease the secretion of CRH and also to the anterior pituitary to decrease the secretion of ACTH resulting in a decrease in circulating glucocorticosteroids. Exogenous corticosteroids, including those absorbed systemically through the skin, may also impart a message to the hypothalamus and anterior pituitary to decrease secretion of hormones. This may result in decreased circulating glucocorticosteroids and thus, a decreased response to glucocorticosteroids.

Assessment of Corticosteroid Effect on HPA Axis Feedback Loop



Low circulating cortisol levels or a decreased response to cortisol are indicative of suppression of the activity of the HPA axis. In order to evaluate the HPA axis function of patients in this study, basal levels of cortisol in the blood will be measured at the end of treatment. Patients will then be injected with Cortosyn™, a synthetic subunit of ACTH. Systemic administration of a synthetic subunit of ACTH should stimulate the Adrenal Cortex to release glucocorticosteroids, unless the patient has had increased circulating levels of glucocorticosteroids for some time and the HPA axis has been suppressed. After 30 minutes have passed blood levels of cortisol will be measured again. Lack of, or limited release of glucocorticosteroids into the blood stream in response to the administered Cortosyn™ will indicate suppression of HPA axis function.

13.6 APPENDIX F

Clinical Laboratory Testing

As part of the Screening Procedures and at Visit 3 (or early termination for randomized patients only) patients will have a blood sample taken for hematology and clinical chemistry testing. The testing panel should include as a minimum the following tests:

Hematology

- Hematocrit
- White blood cell count
- Platelets
- Hemoglobin
- Red blood cell count
- Differential white cell count

Chemistry

- Alkaline phosphatase
- Total bilirubin
- Alanine transaminase
- Creatinine
- Aspartate transaminase
- Glucose
- Blood urea nitrogen

Clinical Laboratory Testing will be performed at a Central Laboratory

ACM Medical Lab, Inc.
160 Elmgrove Park
Rochester, NY 14624, USA

13.7 APPENDIX G

Cortrosyn™ Package Insert

FOR DIAGNOSTIC USE ONLY

CORTROSYN™

(cosyntropin) for Injection

DESCRIPTION

CORTROSYN™ (cosyntropin) for Injection is a sterile lyophilized powder in vials containing 0.25 mg of CORTROSYN™ and 10 mg of mannitol to be reconstituted with 1 mL of 0.9% Sodium Chloride Injection, USP. Administration is by intravenous or intramuscular injection. Cosyntropin is α 1 - 24 corticotropin, a synthetic subunit of ACTH. It is an open chain polypeptide containing, from the N terminus, the first 24 of the 39 amino acids of natural ACTH. The sequence of amino acids in the 1 - 24 compound is as follows:

Ser	Tyr	Ser	Met	Glu	His	Phe	Arg	Trp	Gly	Lys
1	2	3	4	5	6	7	8	9	10	11
Pro	Val	Gly	Lys	Lys	Arg	Arg	Pro	Val	Lys	Val
12	13	14	15	16	17	18	19	20	21	22
Tyr	Pro									
23	24									

CLINICAL PHARMACOLOGY

CORTROSYN™ (cosyntropin) for Injection exhibits the full corticosteroidogenic activity of natural ACTH. Various studies have shown that the biologic activity of ACTH resides in the N-terminal portion of the molecule and that the 1 - 20 amino acid residue is the minimal sequence retaining full activity. Partial or complete loss of activity is noted with progressive shortening of the chain beyond 20 amino acid residues. For example, the decrement from 20 to 19 results in a 70% loss of potency.

The pharmacologic profile of CORTROSYN™ is similar to that of purified natural ACTH. It has been established that 0.25 mg of CORTROSYN™ will stimulate the adrenal cortex maximally and to the same extent as 25 units of natural ACTH. This dose of CORTROSYN™ will produce maximal secretion of 17-OH corticosteroids, 17- ketosteroids and / or 17 - ketogenic steroids.

The extra-adrenal effects which natural ACTH and CORTROSYN™ have in common include increased melanotropic activity, increased growth hormone secretion and an adipokinetic effect. These are considered to be without physiological or clinical significance.

Animal, human and synthetic ACTH (1-39) which all contain 39 amino acids exhibit similar immunologic activity. This activity resides in the C-terminal portion of the molecule and the 22-39 amino acid residues exhibit the greatest degree of antigenicity. In contrast, synthetic polypeptides containing 1-19 or fewer amino acids have no detectable immunologic activity. Those containing 1-26, 1-24 or 1-23 amino acids have very little immunologic although full biologic activity. This property of CORTROSYN™ assumes added importance in view of the known antigenicity of natural ACTH.

INDICATIONS AND USAGE

CORTROSYN™ (cosyntropin) for Injection is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency. Because of its rapid effect on the adrenal cortex it may be utilized to perform a 30-minute test of adrenal function (plasma cortisol response) as an office or outpatient procedure, using only 2 venipunctures (see DOSAGE AND ADMINISTRATION section).

Severe hypofunction of the pituitary - adrenal axis is usually associated with subnormal plasma cortisol values but a low basal level is not per se evidence of adrenal insufficiency and does not suffice to make the diagnosis. Many patients with proven insufficiency will have normal basal levels and will develop signs of insufficiency only when stressed. For this reason a criterion which should be used in establishing the diagnosis is the failure to respond to adequate corticotropin stimulation. When presumptive adrenal insufficiency is diagnosed by a subnormal CORTROSYN™ test, further studies are indicated to determine if it is primary or secondary.

Primary adrenal insufficiency (Addison's disease) is the result of an intrinsic disease process, such as tuberculosis within the gland. The production of adrenocortical hormones is deficient despite high ACTH levels (feedback mechanism). Secondary or relative insufficiency arises as the result of defective production of ACTH leading in turn to disuse atrophy of the adrenal cortex. It is commonly seen, for example, as result of corticosteroid therapy, Sheehan's syndrome and pituitary tumors or ablation.

The differentiation of both types is based on the premise that a primarily defective gland cannot be stimulated by ACTH whereas a secondarily defective gland is potentially functional and will respond to adequate stimulation with ACTH. Patients selected for further study as the result of a subnormal CORTROSYN™ test should be given a 3 or 4 day course of treatment with Repository Corticotropin Injection USP and then retested. Suggested doses are 40 USP units twice daily for 4 days or 60 USP units twice daily for 3 days. Under these conditions little or no increase in plasma cortisol levels will be seen in Addison's disease whereas higher or even normal levels will be seen in cases with secondary adrenal insufficiency.

CONTRAINDICATION

The only contraindication to CORTROSYN™ (cosyntropin) for Injection is a history of a previous adverse reaction to it.

PRECAUTIONS

General

CORTROSYN™ (cosyntropin) for Injection exhibits slight immunologic activity, does not contain animal protein and is therefore less risky to use than natural ACTH. Patients known to be sensitized to natural ACTH with markedly positive skin tests will, with few exceptions, react negatively when tested intradermally with CORTROSYN™. Most patients with a history of a previous hypersensitivity reaction to natural ACTH or a pre-existing allergic disease will tolerate CORTROSYN™. Despite this however, CORTROSYN™ is not completely devoid of immunologic activity and hypersensitivity reactions including rare anaphylaxis are possible. Therefore, the physician should be prepared, prior to injection, to treat any possible acute hypersensitivity reaction.

Drug Interactions

Corticotropin may accentuate the electrolyte loss associated with diuretic therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility. A study in rats noted inhibition of reproductive function like natural ACTH.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with CORTROSYN™ (cosyntropin) for Injection. It is also not known whether CORTROSYN™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. CORTROSYN™ should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CORTROSYN™ (cosyntropin) for Injection is administered to a nursing woman.

Pediatric Use

(See DOSAGE AND ADMINISTRATION section.)

ADVERSE REACTIONS

Since CORTROSYN™ (cosyntropin) for Injection is intended for diagnostic and not therapeutic use, adverse reactions other than a rare hypersensitivity reaction are not anticipated. A rare hypersensitivity reaction usually associated with a pre-existing allergic disease and/or a previous reaction to natural ACTH is possible. Symptoms may include slight whealing with splotchy erythema at the injection site. There have been rare reports of anaphylactic reaction. The following adverse reactions have been reported in patients after the administration of CORTROSYN™ and the association has been neither confirmed nor refuted:

- bradycardia
- tachycardia
- hypertension
- peripheral edema
- rash

DOSAGE AND ADMINISTRATION

CORTROSYN™ (cosyntropin) for Injection may be administered intramuscularly or as a direct intravenous injection when used as a rapid screening test of adrenal function. It may also be given as an intravenous infusion over a 4 to 8 hour period to provide a greater stimulus to the adrenal glands. Doses of CORTROSYN™ 0.25 to 0.75 mg have been used in clinical studies and a maximal response noted with the smallest dose.

A suggested method for a rapid screening test of adrenal function has been described by Wood and Associates (1). A control blood sample of 6 to 7 mL is collected in a heparinized tube. Reconstitute 0.25 mg of CORTROSYN™ with 1mL of 0.9% Sodium Chloride Injection, USP and inject intramuscularly. The reconstituted drug product should be inspected visually for particulate matter and discoloration prior to injection. Reconstituted CORTROSYN™ should not be retained. In the pediatric population, aged 2 years or less, a dose of 0.125 mg will often suffice. A second blood sample is collected exactly 30 minutes later. Both blood samples should be refrigerated until sent to the laboratory for determination of the plasma cortisol response by some appropriate method. If it is not possible to send them to the laboratory or perform the fluorimetric procedure within 12 hours, then the plasma should be separated and refrigerated or frozen according to need.

Two alternative methods of administration are intravenous injection and infusion. CORTROSYN™ can be injected intravenously in 2 to 5 mL of saline over a 2-minute period. When given as an intravenous infusion: CORTROSYN™, 0.25 mg may be added to glucose or saline solutions and given at the rate of approximately 40 micrograms per hour over a 6-hour period. It should not be added to blood or plasma as it is apt to be inactivated by enzymes. Adrenal response may be measured in the usual manner by determining urinary steroid excretion before and after treatment or by measuring plasma cortisol levels before and at the end of the infusion. The latter is preferable because the urinary steroid excretion does not always accurately reflect the adrenal or plasma cortisol response to ACTH.

The usual normal response in most cases is an approximate doubling of the basal level, provided that the basal level does not exceed the normal range. Patients receiving cortisone, hydrocortisone or spironolactone should omit their pre-test doses on the day selected for testing. Patients taking inadvertent doses of cortisone or hydrocortisone on the test day and patients taking spironolactone or women taking drugs which contain estrogen may exhibit abnormally high basal plasma cortisol levels.

A paradoxical response may be noted in the cortisone or hydrocortisone group as seen in a decrease in plasma cortisol values following a stimulating dose of CORTROSYN™.

In the spironolactone or estrogen group only a normal incremental response is to be expected. Many patients with normal adrenal function, however, do not respond to the expected degree so that the following criteria have been established to denote a normal response:

1. The control plasma cortisol level should exceed 5 micrograms/100 mL.
2. The 30-minute level should show an increment of at least 7 micrograms/100 mL above the basal level.
3. The 30-minute level should exceed 18 micrograms/100 mL. Comparable figures have been reported by Greig and co-workers (2).

Plasma cortisol levels usually peak about 45 to 60 minutes after an injection of CORTROSYN™ and some prefer the 60-minute interval for testing for this reason. While it is true that the 60-minute values are usually higher than the 30-minute values, the difference may not be significant enough in most cases to outweigh the disadvantage of a longer testing period. If the 60-minute test period is used, the criterion for a normal response is an approximate doubling of the basal plasma cortisol value.

In patients with a raised plasma bilirubin or in patients where the plasma contains free hemoglobin, falsely high fluorescence measurements will result. The test may be performed at any time during the day but because of the physiological diurnal variation of plasma cortisol the criteria listed by Wood cannot apply. It has been shown that basal plasma cortisol levels and the post CORTROSYN™ increment exhibit diurnal changes. However, the 30-minute plasma cortisol level remains unchanged throughout the day so that only this single criterion should be used (3).

Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit. Reconstituted CORTROSYN™ should not be retained.

HOW SUPPLIED

Box of 10 vials of CORTROSYN™ (cosyntropin) for Injection 0.25 mg

NDC # 0548-5900-00

Storage

Store at 15-30°C (59-86°F).

CORTROSYN™ is intended as a single dose injection and contains no antimicrobial preservative. Any unused portion should be discarded.

Rx only

REFERENCES

1. Wood, J.B. et al. LANCET 1.243, 1965.
2. Greig, W.R. et al. J. ENDOCR 34.411, 1966.
3. McGill, P.E. et al. ANN RHEUM DIS 26.123, 1967.

Amphastar Pharmaceuticals, Inc.
Rancho Cucamonga, CA 91730 U.S.A. REV. 9-05

13.8 APPENDIX H:

Investigator Brochure, Desoximetasone 0.25% Shampoo

Amendment	Date	
1	06/28/16	
The following revisions were made to the protocol Revision 0 dated 04/18/16: • The percent scalp affected was changed to 20% • Stopping criteria for HPA axis suppression was updated for patients with suppression at Visit 1		