1.0 TITLE PAGE

Drug	Desoximetasone 0.15% Topical Spray
Design	An open label, safety study to assess the potential for adrenal suppression following treatment with desoximetasone 0.15% topical spray in patients with atopic dermatitis
Population	Patients with a confirmed diagnosis of atopic dermatitis with 10-30 % body surface area affected Patients will be enrolled in the following Cohorts: • **Cohort 1** –ages 12-17 years of age • **Cohort 2** –ages 6-11 years of age • **Cohort 3** –ages 2-5 years of age • **Cohort 4** – patients 6 months - 1 year old
Sponsor	Taro Pharmaceuticals U.S.A., Inc. 3 Skyline Drive Hawthorne, NY 10532
Protocol Number	DSXS 1502a
Novum Study Number	71615002
IND #	101789
Protocol Date	5/17/2016
Protocol Date Rev1	6/27/2016
Protocol Date Rev2	9/06/2016

NIIRB
September 13, 2016
APPROVED

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SIGNATURE PAGE

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

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Date

PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol DSXS 1502a Rev2 in accordance with FDA regulations, ICH guidelines and Good Clinical Practice. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Taro Pharmaceuticals, USA) or Novum Pharmaceutical Research Services, the company managing the study.

_____ _____

Principal Investigator Date

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4.0 SYNOPSIS

Protocol Number	DSXS 1502a
Title	An Open Label, Safety Study to Assess the Potential for Adrenal Suppression Following Treatment with Desoximetasone 0.15% Topical Spray (Taro Pharmaceuticals U.S.A., Inc.) in Patients with Atopic Dermatitis
Objectives	1. The objective of this study is to evaluate the potential of desoximetasone 0.15% topical spray to suppress HPA axis function in patients with moderate to severe atopic dermatitis. 2. The secondary objectives are to evaluate to evaluate the efficacy parameters and adverse event (AE) profiles of desoximetasone 0.15% topical spray administered to patients with moderate to severe atopic dermatitis.
Sponsor	Taro Pharmaceuticals U.S.A., Inc.
Name of Test Product	Desoximetasone 0.15% Topical Spray
Route of Administration	Topical
Study Design	An open label, safety study to assess the potential for adrenal suppression following treatment with desoximetasone 0.15% topical spray admininstered twice daily for 28 days in patients with moderate to severe atopic dermatitis
Study Population	Approximately twenty-five (25) to fifty (50) patients stratified by age with a confirmed diagnosis of moderate to severe atopic dermatitis with: **Cohort 1 –** 10-20 patients age 12-17 years of age with 10-30% body surface area (BSA) affected **Cohort 2 –** 5-10 patients age 6-11 years of age with 10-30% body surface area (BSA) affected **Cohort 3 –** 5-10 patients age 2-5 years of age with 10-30% body surface area (BSA) affected **Cohort 4 –** 5-10 patients 6 months- 1 year of age with 10-30% body surface area (BSA) affected Cohorts will be enrolled in sequential order. Each cohort will initiate enrollment once the previous cohort has reached the minimum number of patients and a safety analysis has been reviewed. Each cohort will be enrolled based on the availability of patients. Each cohort will be reviewed for the potential of HPA axis suppression. If at

	least 50% of patients in each Cohort experience HPA axis suppression once the minimum number of patients has been enrolled and completed the cohort, enrollment for that cohort will be stopped and no further cohorts will be initiated. If at least 35% of patients have experienced HPA axis suppression across cohorts combined during the study, enrollment will be discontinued and no other cohorts will be initiated. Cohort 2 will not begin until safety data has been reviewed for Cohort 1. The same process will be followed for each Cohort until the study is complete. The enrollment in the individual Cohort may not require if the satisfactory safety data for the same age group was obtained in the study DSXS 1502.
Study Conduct	All patients will attend the clinic for 3 scheduled visits: **Visit 1:** Screening/Enrollment (Day 1) **Visit 2:** Interim Visit (Day 14 ± 2) **Visit 3:** End of Study (Day 29 ± 2) or Early Termination
Inclusion Criteria	1. Male or non-pregnant, non-lactating females: • **Cohort 1** –ages 12-17 years of age • **Cohort 2** –ages 6-11 years of age • **Cohort 3** –ages 2-5 years of age • **Cohort 4** – patients 6 months - 1 year of age 2. If female and of child-bearing 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) 3. Parent/legal guardian has signed informed consent form, which meets all criteria of current FDA regulations. 4. Based on the patient's age, 11 -17 year olds will read and sign an IRB approved assent form. Patients 6-10 years of age will provide verbal assent to participate. 5. Patients with a definite clinical diagnosis of stable atopic dermatitis with involvement of: • **Cohort 1** –age 12-17 years of age with 10-30% body surface area (BSA) affected (excluding face, axilla and groin areas) • **Cohort 2** – age 6-11 years of age with 10-30% body surface area (BSA) affected (excluding face, axilla and groin areas) • **Cohort 3** –age 2-5 years of age with with 10-30% body surface area (BSA) affected (excluding face, axilla and groin areas) • **Cohort 4** – 6 months - 1 year of age with 10-30% body surface area (BSA) affected (excluding face, axilla and groin areas) 6. Have an Eczema Area and Severity Index (EASI) score of at least 15 7. Have an Investigator Global Assessment Scale (IGA) 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. Lacks stable diagnosis of atopic dermatitis or has been diagnosed with mild atopic dermatitis 3. Have an EASI score of < 15. 4. Have an IGA score of < 3. 5. Atopic dermatitis with a BSA involvement of < 10% or < 30%. 6. Active cutaneous bacterial or viral infection in any treatment area at baseline (i.e., clinically infected atopic dermatitis) 7. Patient has a history of atopic dermatitis that has been unresponsive to topical corticosteroid therapy 8. Any condition (i.e., sunburn, psoriasis etc.) that, in the Investigator's opinion, may interfere with the clinical assessments of the signs and symptoms of atopic dermatitis 9. Patient has a history of allergy or sensitivity to corticosteroids or history of any drug hypersensitivity or intolerance which, in the opinion of the Investigator, would compromise the safety of the patient or the results of the study 10. Patient has a significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that, in the Investigator's opinion, would place the study patient at undue risk by participation in the study 11. Patient is currently receiving or has received any radiation therapy, anti-neoplastic agents or immunosuppressant medication within 4 weeks before the first dose of study drug 12. Use within one month before baseline of 1) oral or intravenous corticosteroids, 2) UVA/UVB therapy, 3) PUVA (psoralen plus ultraviolet A) therapy, 4) tanning booths, 5) nonprescription UV light source, 6) immunomodulators or immunosuppressive therapies, 7) interferon, 8) cytotoxic drugs, 9) tacrolimus or 10) pimecrolimus 13. Use within 14 days before baseline of 1) systemic antibiotics, 2) calcipotriene or other Vitamin D preparations, or 3) retinoids 14. Patients who have used topical treatments, prescription or over the counter, including: a. Any topical atopic dermatitis therapeutic agents of any kind within the 2 weeks before first use of study drug b. Any topical corticosteroids within the 2 weeks before the first use of the study drug c. Any antibacterial, medicated and/or astringent washes, soaps, pads or moisturizers within the 3 days before the first use of study drug. d. High strength (20% or above) alpha-hydroxy acid or any kind of peel or other procedures on the face (e.g., laser hair removal) within 30 days of the study start e. Any topical products (i.e., sunscreens, lotions, creams), except for

	bland emollient (moisturizer) within 24 hour before baseline f. Topical antibiotics in the treatment area within 7 days before baseline 15. Patient has been treated within 12 weeks (or five half lives, whichever is less) before the first dose of study drug with any biological therapies for atopic dermatitis 16. Use of non-sedating anti-histamines within the 7 days before the first dosing day The use of sedating anti-histamines, such as diphenhydramine, may be acceptable on condition the patient has been on a stable dose for at least 14 days before the study start and will remain on a stable dose throughout the study 17. Any oral steroid drug use (with the exception contraceptives) within 28 days of the first dosing day or during the study a. Female patients using hormonal contraceptives should have been on the same product/dosing regimen for at least 28 days before and should not change this regimen during the study b. The use of inhaled or intranasal corticosteroids is acceptable as long as usage has been stable for at least 2 weeks before the first dose of study drug and will be continued during the study 18. Inability to understand the protocol requirements, instructions, and study-related restrictions, the nature, scope, and possible consequences of the clinical study. 19. 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. 20. Receipt of any drug as part of a research study within 30 days prior to first dosing. 21. The patient is a member of the investigational study staff or a member of the family of the investigational study staff. 22. Previous participation in this study including patients previously enrolled in DSXS 1502.
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 **Secondary Outcome Measures:** Hypothalamic Pituitary Adrenal (HPA) Axis Response to Cosyntropin demonstrating the presence of adrenal suppression at the end of treatment with % BSA as a covariate

HPA Axis Evaluation	Prior to the first dose of study drug and at the end of the study (Day 28 or early termination) all patients will have a cortisol response test performed using the procedure of Wood et al. (See Appendix E). Only those patients with normal adrenal function at baseline will be enrolled and dispensed study drug. 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 test at least every 4 weeks until such time as the Investigator considers the adrenal function has turned to normal. Cohorts will be enrolled in sequential order. Each cohort will initiate enrollment once the previous cohort has reached the minimum number of patients and a safety analysis has been reviewed. Each cohort will be enrolled based on the availability of patients. Each cohort will be reviewed for the potential of HPA axis suppression. If at least 50% of patients in each Cohort experience HPA axis suppression, enrollment for that cohort will be stopped and no further cohorts will be initiated. If at least 35% of patients have experienced HPA axis suppression across cohorts combined during the study, enrollment will be discontinued and no other cohorts will be initiated. Cohort 2 will not begin until safety data has been reviewed for Cohort 1. The same process will be followed for each Cohort until the study is complete. **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 % BSA affected as a covariate.
Safety Parameters	Adverse events will be classified using standard MedDRA terminology Version 19.0 or higher and summarized by treatment group. Summary tables comparing the type, incidence, severity and Investigator's opinion of relationship to the study drug will be prepared by treatment group. Signs and symptoms of atopic dermatitis 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. If sufficient data exist, adverse event frequencies will be compared between treatments using Fisher's exact test or a similar test. Concomitant medication use during the study will be tabulated by patient. Adverse events reported during the study will be tabulated in a summary

	table listing the type, incidence, severity and Investigator's opinion to drug relationship.
Sample Size Determination	The sample size of 25 to 50 patients, stratified by age and % BSA, was determined to be sufficient for this study.

5.0 STUDY SCHEMATIC

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
Day	**1**	**14±2**	**29±2**	**42±4**
Procedures	Enrollment **Before 12 pm**	Interim Visit	End of Study/Early Termination **Before 12 pm**	Telephone Follow-Up Visit
Informed Consent	X			
Medical History and Demographics	X			
Vital Signs	X	X	X	
Pregnancy Test*	X	X	X	
Physical Exam	X		X	
% BSA Assessment	X	X	X	
IGA Score	X	X	X	
EASI Score	X	X	X	
Application Site Reactions	X	X	X	
Concomitant Medication	X	X	X	
Laboratory Evaluations	X		X	
Cortisol Response Test	X		X	
Confirm Inclusion/Exclusion Criteria	X			
Dispense Sunscreen and Wristband	X			
Weigh and Dispense Study Drug	X	X		
Collect and Weigh Study Drug		X	X	
Dispense/Review Patient Diary	X	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 0.15% topical spray. This product contains a potent corticosteroid to be indicated for the treatment of patients with moderate to severe atopic dermatitis.

7.1 Disease Being Treated

Atopic dermatitis (AD), commonly known as eczema, is a chronic inflammatory skin condition affecting approximately 17.8 million people in the United States.[1] It is characterized by itchy, erythematous, and scaly skin lesions often localized to the flexural surfaces of the body, including neck, eyelids, forehead, face, wrists, dorsa of the feet, and hands. AD is also associated with secondary skin infections with *S. aureus* and herpes simplex virus (HSV).[2] Onset of AD typically occurs at an early age, and a 2003 survey of children in the United States estimated an overall prevalence of approximately 11%, and as high as 19% in some states. In the United States alone, it is estimated that more than $364 million per year is spent on the treatment of childhood atopic dermatitis.[1]

AD can present in three clinical phases, viz. acute, sub-acute and chronic. It can be differentially diagnosed as contact dermatitis, candidiasis, psoriasis, scabies, impetigo etc due to its appearance and presentation on skin. Diagnosis of AD is based on history and physical examination. There are many proposed diagnostic criteria; however, a 2008 systematic review concluded that the U.K. Working Party's Diagnostic Criteria are the most extensively validated. The most important features considered for AD diagnosis are pruritus, eczema, body surface area involvement and pattern, along with medical history and associated features.[3] A commonly used disease severity scale for clinical studies in AD is the Eczema Area and Severity Index (EASI) which uses objective physician estimates of disease extent and severity. The Investigator's Global Assessment (IGA) is also used, typically as a static measure, to score the severity of signs and symptoms of AD. [4,5]

Recent research indicates that some of the causative factors for AD include an impaired skin barrier, allergies, complex immune dysregulation and IgE-mediated inflammatory pathways. Genetic associations of AD have also been indicated, including mutation of the pro-filaggrin (*FLG*) gene; responsible for a key structural protein of the upper epidermal layer of skin.[6,7]

7.2 Availability and Efficacy of Already Approved Therapies

The Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology established guidelines for AD therapy in 2012.[5] According to these guidelines, the first line management of AD must include a combination of skin hydration, topical corticosteroids, calcineurin inhibitors/tacrolimus (Protopic®, Elidel®), over the counter (OTC) tar preparations, antihistamines, Vitamin D or dilute bleach baths. Topical corticosteroids (creams, gels, emulsions, lotions) remain the first choice of therapy for management of mild-severe forms of AD.[8] Antimicrobials (oral ± topical) are recommended to treat secondary infections in AD. Immunomodulating agents, such as

cyclosporine, mycophenolate mofetil, azathioprine, IFN-g, and corticosteroids, have been shown to provide benefit for patients with severe refractory AD; however, many of them are associated potential serious adverse effects.[1,5,7,8]

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

7.3 Scientific and Statistical Considerations

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 E, F).[9] Recovery from steroid-induced adrenal insufficiency is usually rapid after the treatment is withdrawn.[10] See Appendix E for further explanation of the evaluation of the role of topical corticosteroids in HPA axis suppression.

Taro Pharmaceuticals USA 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.[9, 12, 13, 14, 15, 17]

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 children may benefit from its use.

The potential risks and benefits of participation in the study will be explained to the patient and parent or legal guardian 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

1. The primary objective of this study is to evaluate the potential of desoximetasone 0.15% topical spray to suppress HPA axis function in patients with moderate to severe atopic dermatitis.
2. The secondary objectives are to evaluate the efficacy parameters and adverse event (AE) profile of desoximetasone 0.15% topical spray administered to patients with moderate to severe atopic dermatitis.

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 treatment with desoximetasone 0.15% topical spray (Taro Pharmaceuticals, U.S.A.), for the treatment of moderate to severe atopic dermatitis.

Approximately 25 to 50 eligible patients with atopic dermatitis 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 atopic dermatitis with IGA score of at least 3 or 4.

Approximately twenty-five (25) to fifty (50) patients stratified by age with a confirmed diagnosis of moderate to severe atopic dermatitis with:
Cohort 1 – 10 -20 patients age 12-17 years of age with 10-30% body surface area (BSA) affected
Cohort 2 – 5-10 patients age 6-11 years of age with 10-30% body surface area (BSA) affected
Cohort 3 – 5-10 patients age 2-5 years of age with 10-30% body surface area (BSA) affected
Cohort 4 – 5-10patients 6 months to 1 year of age with 10-30% body surface area (BSA) affected

Cohorts will be enrolled in sequential order. Each cohort will initiate enrollment once the previous cohort has reached the minimum number of patients and a safety analysis has been reviewed. Each cohort will be enrolled based on the availability of patients.

Each cohort will be reviewed for the potential of HPA axis suppression. If at least 50% of patients in a Cohort experience HPA axis suppression, enrollment for that cohort will be stopped and no further cohorts will be initiated. If at least 35% of patients have experienced HPA axis suppression across all cohorts combined during the study, enrollment will be discontinued and no

other cohorts will be initiated. Cohort 2 will not begin until safety data has been reviewed for Cohort 1. The same process will be followed for each Cohort until the study is complete. The enrollment in the individual Cohort may not be required if the satisfactory safety data for the same age group was obtained in the study DSXS 1502.

Patients enrolled in the study will apply product twice a day, according to provided instructions, for a total of 28 days.

Patients will attend a total of 3 Clinic Visits as follows:

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

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 open label, safety study to assess the potential of desoximetasone 0.15% topical spray to suppress HPA axis function was based on recommendations provided by the FDA in IND 101789 Guidance Meeting (01/14/2015, Reference ID 3689041), regarding the scope and design of studies for desoximetasone 0.15% spray and an FDA Advice Letter dated 04/27/2015.[15, 17]

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Male or non-pregnant, non-lactating females:
   - **Cohort 1** –ages 12-17 years of age
   - **Cohort 2** –ages 6-11 years of age
   - **Cohort 3** –ages 2-5 years of age
   - **Cohort 4** – 6 months - 1 year of age
2. If female and of child-bearing 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)
3. Parent/legal guardian has signed informed consent form, which meets all criteria of current FDA regulations.
4. Based on the patient's age 11 -17 years old will read and sign an IRB approved assent form. Patients 6-10 years of age will provide verbal assent to participate.
5. Patients with a definite clinical diagnosis of stable atopic dermatitis with involvement of:
   - **Cohort 1** –age 12-17 years of age with 10-30% body surface area (BSA) affected (excluding face, axilla and groin areas)

- **Cohort 2 –** age 6-11 years of age with 10-30% body surface area (BSA) affected (excluding face, axilla and groin areas)
- **Cohort 3 –**age 2-5 years of age with 10-30% body surface area (BSA) affected (excluding face, axilla and groin areas)
- **Cohort 4 –**6 months – 1 year of age with 10-30% body surface area (BSA) affected (excluding face, axilla and groin areas)

6. Have an Eczema Area and Severity Index (EASI) score of at least 15
7. Have an Investigator Global Assessment Scale (IGA) 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. Lacks stable diagnosis of atopic dermatitis or has been diagnosed with mild atopic dermatitis
3. Have an EASI score of < 15.
4. Have an IGA score of < 3.
5. Atopic dermatitis with a BSA involvement of < 10% or > 30%.
6. Active cutaneous bacterial or viral infection in any treatment area at baseline (i.e., clinically infected atopic dermatitis)
7. Patient has a history of atopic dermatitis that has been unresponsive to topical corticosteroid therapy
8. Any condition (i.e., sunburn, psoriasis etc.) that, in the Investigator's opinion, may interfere with the clinical assessments of the signs and symptoms of atopic dermatitis
9. Patient has a history of allergy or sensitivity to corticosteroids or history of any drug hypersensitivity or intolerance which, in the opinion of the Investigator, would compromise the safety of the patient or the results of the study
10. Patient has a significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that, in the Investigator's opinion, would place the study patient at undue risk by participation in the study
11. Patient is currently receiving or has received any radiation therapy, anti-neoplastic agents or immunosuppressant medication within 4 weeks before the first dose of study drug
12. Use within one month before baseline of 1) oral or intravenous corticosteroids, 2) UVA/UVB therapy, 3) PUVA (psoralen plus ultraviolet A) therapy, 4) tanning booths, 5) nonprescription UV light source, 6) immunomodulators or immunosuppressive therapies, 7) interferon, 8) cytotoxic drugs, 9) tacrolimus or 10) pimecrolimus
13. Use within 14 days before baseline of 1) systemic antibiotics, 2) calcipotriene or other Vitamin D preparations, or 3) retinoids
14. Patients who have used topical treatments, prescription or over the counter, including:
    a. Any topical atopic dermatitis therapeutic agents of any kind within the 2 weeks before first use of study drug
    b. Any topical corticosteroids within the 2 weeks before the first use of the study drug
    c. Any antibacterial, medicated and/or astringent washes, soaps, pads or moisturizers within the 3 days before the first use of study drug.
    d. High strength (20% or above) alpha-hydroxy acid or any kind of peel or other procedures on the face (e.g., laser hair removal) within 30 days of the study start

e. Any topical products (i.e., sunscreens, lotions, creams), except for bland emollient (moisturizer) within 24 hour before baseline
f. Topical antibiotics in the treatment area within 7 days before baseline

15. Patient has been treated within 12 weeks (or five half lives, whichever is less) before the first dose of study drug with any biological therapies for atopic dermatitis
16. Use of non-sedating anti-histamines within the 7 days before the first dosing day
    The use of sedating anti-histamines, such as diphenhydramine, may be acceptable on condition the patient has been on a stable dose for at least 14 days before the study start and will remain on a stable dose throughout the study
17. Any oral steroid drug use (with the exception contraceptives) within 28 days of the first dosing day or during the study
    a. Female patients using hormonal contraceptives should have been on the same product/dosing regimen for at least 28 days before and should not change this regimen during the study
    b. The use of inhaled or intranasal corticosteroids is acceptable as long as usage has been stable for at least 2 weeks before the first dose of study drug and will be continued during the study
18. Inability to understand the protocol requirements, instructions, and study-related restrictions, the nature, scope, and possible consequences of the clinical study.
19. 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.
20. Receipt of any drug as part of a research study within 30 days prior to first dosing.
21. The patient is a member of the investigational study staff or a member of the family of the investigational study staff.
22. Previous participation in this study including patients previously enrolled in DSXS 1502.

9.3.3 Restrictions during the Study

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

- Any prescription or over-the-counter (OTC) topical, systemic, phototherapy or biological medications or treatments for AD.
- Any non-steroidal immunosuppressants (by any route of administration)
- Use of non-sedating anti-histamines
  - The use of sedating anti-histamines, such as diphenhydramine, may be acceptable on condition the patient has been on a stable dose for at least 14 days before enrollment and will remain on a stable dose throughout the study.
- Any oral, topical or injectable steroid drug use (with the exception of HRT and contraceptives).

- Female patients using hormonal contraceptives or HRT should have been on the same product/dosing regimen for at least 4 weeks before and should not change this during the study.

- New regimens of inhaled corticosteroids.
  - Inhaled or intranasal corticosteroids are permissible, provided that the patient has been on a stable regimen for at least 2 weeks before the first dose of study drug and will continue during the study.

- Any other treatments, prescription or over-the-counter products for the treatment of any other dermatological condition including; topical corticosteroids**,** antibacterial, medicated and/or astringent washes, soaps, pads or moisturizers during the study.

- Use of high strength (20% or above) alpha-hydroxy acid or any kind of peel or other procedures on the treatment areas (laser hair removal) during the study.

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

Patients and parents/legal guardians will be instructed not to apply the medication to the face, groin or axilla and not to use occlusive dressings on the treatment area.

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

9.3.4 Removal of Patients from the Study

Patients and parents/legal guardians 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 AD
- 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 after enrollment will be evaluated for safety and will be given, or referred for, appropriate treatment.

9.4 Treatments

9.4.1 Treatments Administration

The patient or parent/legal guardian will be instructed to apply and rub in gently a thin film of the study drug to the affected areas twice daily (morning and evening) for 28 days. The hands should be washed after applying the drug.

To ensure compliance with the dosing technique, the patient or parent/legal guardian will be instructed to apply the first dose of medication under staff supervision at the time of enrollment and then twice daily until the patient's next scheduled visit. Patient or parents/legal guardians will be instructed not to apply the study drug within 12 hours of the visit which includes the Cortisol Response Test. The patient or parent/legal guardian will be instructed not to apply the medication to the face, axilla or groin and not to use occlusive dressings on the treatment area. Each patient or parent/legal guardian will be provided with a dosing diary in which they will be required to record dosing dates and times. These diaries should be brought to each visit in order that the study staff may check compliance. At the end of the study, the dosing diaries will be retained in the patient's file as source documentation.

At Visit 1 (Screening/Enrollment) and Visit 2 (Interim Visit) qualified study patients or parents/legal guardians will be provided with one 100 ml bottle of desoximetasone 0.15% topical spray along with instructions for dosing. This bottle should be weighed before dispensing and the weight recorded. At Visit 2 (Interim Visit), the bottle should be collected**,** weighed and the weight recorded. A new 100 ml bottle of desoximetasone 0.15% topical spray should be weighed and the weight recorded before dispensing the spray bottle along with dosing instructions to the patient or parent/legal guardian. This bottle should be weighed and the weight recorded upon returnat Visit 3 (End of Study/End of Treatment).

Treatment compliance will be encouraged by instructing the patient or parent/legal guardian 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

All study drugs will be provided by Taro Pharmaceuticals U.S.A., Inc. Each patient will receive 2 x 100 mL bottles of desoximetasone 0.15% topical spray.

The study medication will be shipped to each Investigator's site from a centralized pharmacy. The Principal Investigator at each site is responsible for ensuring that all study medications are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study medication will be maintained in accordance with federal regulations.

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

9.4.3 Method of Assigning Patients to Treatment Groups

Patients eligible for enrollment into the study will fall into one of five cohorts:

Cohort 1 – 10 -20 patients age 12-17 years of age with 10-30% body surface area (BSA) affected
Cohort 2 – 5-10 patients age 6-11 years of age with 10-30% body surface area (BSA) affected
Cohort 3 – 5-10 patients age 2-5 years of age with 10-30% body surface area (BSA) affected
Cohort 4 – 5-10 patients 6 months -1 year of age with 10-30% body surface area (BSA) affected

At Visit 1 eligible patients will be enrolled to the study and assigned a patient number.

Cohorts will be enrolled in sequential order. Each cohort will initiate enrollment once the previous cohort has reached the required number of patients and a safety analysis has been reviewed. Each cohort will be enrolled based on the availability of patients.

Each cohort will be reviewed for the potential of HPA axis suppression. If at least 50% of patients in each Cohort experience HPA axis suppression, enrollment for that cohort will be stopped and no further cohorts will be initiated. If at least 35% of patients have experienced HPA axis suppression across cohorts combined during the study, enrollment will be discontinued and no other cohorts will be initiated. Cohort 2 will not begin until safety data has been reviewed for Cohort 1. The same process will be followed for each Cohort until the study is complete.
The enrollment in the individual Cohort may not be required if the satisfactory safety data for the same age group was obtained in the study DSXS 1502.

9.4.4 Packaging

This is an open label study. The study drug 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 drug supplies received.
- The Investigator or designee will maintain a log of all drug dispensed to and returned by the patients and note the date each drug is returned to the Sponsor.
- The weight of the study drug bottles before dispensing and after collection will be recorded.
- All study drug will be stored at controlled room temperature between 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F), in a secure place with access to authorized individuals only.

- In the event of loss or apparent spoilage of the test preparation, the Investigator or designee must inform the study monitor. If necessary, a properly labeled replacement bottle will be issued to the patient.

9.4.6 Compliance

Patients will be provided with a diary with instructions to record the time and date of dosing. Patients will be asked to also record any adverse events and concomitant medications taken during the study.

Patients will dose twice daily for 28 days. All patients who are enrolled and used at least 75%-125% of scheduled doses of the study drug and have data from a post-treatment cortisol response test will be included in the analysis.

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 (Day 1): Screening/Enrollment, Before 12 pm

1. **Informed Consent:** For patients under the age of majority in the state the study is being conducted (18 years in most states) the parent or legal guardian should sign the consent form and the child (age ≥ 11 years old) will be required to sign a patient "assent" form that will be written in such a way as to be understandable to a child. Patients age 6-10 years of age will provide verbal assent to participate.
2. **Medical History and Demographics**: The patient's demographic and a complete medical history will be obtained for the patient's current and past medical conditions.
3. **Physical Examination and % BSA Assessment:** A general physical exam will be conducted. The patient's body weight (kg) and height (cm) will also be measured while the patient is lightly clothed (e.g., no coat or shoes). %BSA will be assessed using instructions in Appendix A.
4. **Vital Signs:** The patient's vital signs will be taken and recorded (pulse, blood pressure, temperature and respiration rate).
5. **Pregnancy Test:** A urine pregnancy test will be required of all females of child bearing potential prior to enrollment.
6. **Dermatological Assessment:** Clinical signs and symptoms of AD will be evaluated by the Investigator based on the following:
    - EASI Score (Appendix B)
    - IGA Score (Appendix C)
    - Application Site Reactions (Appendix D)
7. **Concomitant Medication:** Review with the patient and parent/legal guardian the patient's use of concomitant medication within the last 12 weeks.
8. **Confirm Inclusion/Exclusion Met:** Confirm the patient meets all inclusion/exclusion criteria pending results of the Cortisol Response Test.

9. **Laboratory Evaluations:** A blood sample will be collected for hematology and clinical chemistry testing. (See Appendix G).
10. **Cortisol Response Test:** All patients will have a cortisol response test performed according to the procedure detailed in Appendix E.
11. **Dispense Study drug**: If patient is eligible to enroll, record the weight of one bottle of study drug and dispense with instructions.
12. **Apply Study Medication:** The first dose of study medication should be administered by the patient (≥12 years of age) or parent/legal guardian at the site, under staff supervision.
13. **Provide Dosing Diary**: Provide Diary and instruct parent/legal guardian regarding how it is to be filled out and how study drug is to be used.
14. **Dispense Sunscreen:** For use only when sun exposure cannot be avoided.
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 child bearing potential prior to enrollment.
2. **Vital Signs:** The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
3. **% BSA Assessment:** % BSA covered with atopic dermatitis will be assessed using instructions in Appendix A.
4. **Dermatological Assessment:** Clinical signs and symptoms of AD will be evaluated by the Investigator based on the following:
    - EASI Score (Appendix B)
    - IGA Score (Appendix C)
    - Application Site Reactions (Appendix D)
5. **Concomitant Medication:** Review with the patient and parent/legal guardian the patient's use of new or change in ongoing concomitant medication since Visit 1.
6. **Adverse Events:** Patients will be questioned about any health status changes/adverse events since last visit. All events will be recorded.
7. **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 and parents/legal guardians on dosing requirements of the study.
8. **Collect Study Drug:** The used bottle of study drug will be collected and the weight recorded.
9. **Dispense Study drug**: If patient continues in the study, record weight of one bottle of study drug and dispense.

10. **Provide Dosing Diary:** If patient continues in the study, provide a new dosing diary. Instruct parents/legal guardians not to apply dose to patient within approximately 12 hours of 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 prior to enrollment.
3. **Physical Exam:** A general physical exam will be conducted.
4. **% BSA Assessment:** % BSA covered with atopic dermatitis will be assessed using instructions in Appendix A.
5. **Dermatological Assessment:** Clinical signs and symptoms of AD will be evaluated by the Investigator based on the following:
    - EASI Score (Appendix B)
    - IGA Score (Appendix C)
    - Application Site Reactions (Appendix D)
6. **Concomitant Medication:** Review with the patient and parent/legal guardian the patient's use of new or change in ongoing concomitant medication since Visit 2.
7. **Adverse Events:** Patients will be questioned about any health status changes/adverse events since last visit. All events will be recorded.
8. **Evaluation of Patient Compliance to the Protocol**: Collect and review patient's dosing diary for compliance. Non-compliance with dosing does not warrant dismissal from the study.
9. **Collect Study Drug:** The used bottle of study drug will be collected and the weight recorded.
10. **Laboratory Evaluations:** A blood sample will be collected for hematology and clinical chemistry testing. (See Appendix G).
11. **Cortisol Response Test:** All patients will have a cortisol response test performed according to the procedure detailed in Appendix E.

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

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

9.6 Study Procedures

9.6.1 Informed Consent

For patients under the age of majority in the state the study is being conducted (18 years in most states) the parent or legal guardian should sign the consent form and for patients 11 years of age or older, an assent form will also be required. For illiterate parents or legal guardians, 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. 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. Patients age 6-10 years of age will provide verbal assent to participate.

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 atopic dermatitis, 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 and % Body Surface Area (BSA)

A general physical exam will be conducted at Visit 1 and Visit 3. At Visit 1 the patient's height (meters) and weight (kg) will be measured. The height and weight will be recorded and the Body Surface Area (BSA) will be calculated (see Appendix A for conversions from inches and pounds as appropriate). At Visit 1, 2, and 3, the % BSA affected will be recorded (see Appendix A).

9.6.6 Dermatological Assessment

At Visit 1 a visual inspection to confirm a diagnosis of moderate to severe atopic dermatitis will be done. At each visit atopic dermatitis will be assessed according to the following measures:

- IGA Score : Appendix C
- Signs and Symptoms Assessments and EASI Score: Appendix B
- Application Site Reactions (Appendix D)

Patients will also be asked to rate the severity of pruritus over the previous 24 hours using scale provided in Appendix B. Whenever possible, the same Investigator should perform dermatological assessments for a given patient.

9.6.7 Concomitant Medication Use

At Visits 1-3 patients will be questioned about current and concomitant medication use over the previous 12 weeks. At all visits patients will be questioned about ongoing or new concomitant medication use.

9.6.8 Pregnancy Test

Urine pregnancy tests on females of child-bearing 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.

9.6.9 Dispensing Study Drug

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

The weight of the study drug product should be recorded before dispensing. **The patient will be instructed to apply the first dose of study drug during Visit 1 under staff supervision.**

9.6.10 Collecting Study Drug

Study medication bottles will be collected and weighted at Visits 2 and 3.

9.6.11 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.

9.6.12 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.

9.6.13 Standard Sunscreen and Patient Wristband

All patients will be advised to avoid sun exposure. A standard sunscreen will be provided at Visit 1 should the use of sunscreen be warranted. 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.

9.6.14 Laboratory Evaluation

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

9.6.15 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 E. The resulting blood sample should be sent to ACM Global Laboratory for immediate testing.

Visit 3 Test

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); in case of 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 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. As 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 (AE). 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 due to interference with age-appropriate instrumental ADL (Activities of Daily Living), for example preparing for meal, shopping for groceries or clothing, using the telephone, etc. the patient will be followed until the AE resolves or is considered stable. Any subject that discontinues the study due to an adverse event will be followed until resolution or stabilization of the adverse event.

9.8 Serious Adverse Events

9.8.1 Definition of a Serious Adverse Event

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

- Results in death – includes all deaths, even those that appear to be completely unrelated to study treatment (e.g., car accident where patient is a passenger).
- Is life–threatening – in the view of the Investigator, the patient is at immediate risk of death at the time of the event.
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Causes congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the serious outcomes listed above (e.g., intensive treatment in an emergency room, convulsions that do not result in hospitalizations). Emergency Room visits that require medical or surgical intervention to prevent one of the other serious outcomes listed above are considered a Serious Adverse Event.

9.8.2 Reporting Serious Adverse Events

Investigator Reporting of SAEs

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

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

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

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

Novum will report any Serious Adverse Event to Taro.

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

Taro Study Manager:	Taro Drug Safety Manager:
Natalie Yantovskiy	Margo Lacy Wyatt, RN, BSN,
Director, Clinical Research	Associate Director, Drug Safety
Taro Pharmaceuticals U.S.A., Inc.	Taro Pharmaceuticals U.S.A., Inc.
3 Skyline Drive	3 Skyline Drive, Hawthorne, NY 10532
Hawthorne, NY 10532	914-345-9001 Ext. 6758
Phone: (914) 345-9001 x6293	Email: Margo.Wyatt@taro.com
Email: Angella.Silye@Taro.com	and TAROPVUS@TARO.com

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

10.0 STATISTICAL METHODS

10.1 Statistical Plan

A Statistical Analysis Plan (SAP), detailing the intended statistical analysis of the study data, will be prepared as a separate document and finalized prior to 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 35 patients, stratified by age and % BSA, was determined to be sufficient.

10.1.2 Baseline Comparability

Baseline comparability of the two groups will be assessed using appropriate statistical tests (e.g., one-way analysis of variance, Fisher's exact test, Cochran-Mantel-Haenszel test). The groups will be compared for basic demographics (age, gender, ethnicity and race), baseline IGA, baseline EASI score and baseline total BSA. Summary tables by group will be presented.

10.1.3 Safety Analysis of Potential HPA Axis Suppression

Dosing will be twice a day for 28 days excluding the doses prior to the Cortisol Response Test (54 applications). All patients who are enrolled, use at least 42 doses of the study drug and have data

from a post-treatment cortisol response test will be included in the analysis. Patients who have not used 42 doses of the study drug will be excluded from the primary analysis of HPA axis suppression.

The primary analysis of interest is the proportion of patients in each group who are 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 %BSA affected as a covariate. See Appendix E for results from the cortisol response test considered indicative of potential HPA axis suppression.

The study will be enrolled by Cohort starting with Cohort 1 and each cohort will be reviewed for the potential of HPA axis suppression. If at least 50% of patients in Cohort 1 experience HPA axis suppression once the minimum number of patients has been enrolled and completed the cohort, enrollment for that cohort will be stopped and no further cohorts will be initiated. If at least 35% of patients have experienced HPA axis suppression across cohorts combined during the study, enrollment will be discontinued and no other cohorts will be initiated. Cohort 2 will not begin until safety data has been reviewed for Cohort 1. The same process will be followed for each Cohort until the study is complete.

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

10.2 Safety Analysis

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

Adverse medical events experienced by the patients will be tabulated. The relationship of AEs, if any, to the study drug 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 59th World Medical Association General Assembly, October 2013.

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's parent/legal guardian before enrollment into the study. In addition, subjects 11-17 years of age will be presented with an Assent Form. 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 parent/legal guardian will be asked to give consent by signing and dating the ICF/Assent Form and the patient will be asked to give assent by signing and dating in the appropriate areas of the Assent. 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 drug will be stored at controlled room temperature 15-30°C (59-86ºF), in a secure place with access by authorized individuals only. The Investigator will be responsible for maintaining accurate records of drug receipt, dispensing, and return. At the end of the study, all partially used and unused study drug 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 child bearing potential must be advised of the importance of avoiding pregnancy during study participation.

A negative result of a urine pregnancy test having a minimum sensitivity of at least 25 mIU/ml for hCG should be obtained, 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.

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 Berke, R., Singh, A. & Guralnick, M. Atopic dermatitis: an overview. *American family physician* **86**, 35-42 (2012).

2 Ong, P. Y. & Leung, D. Y. The infectious aspects of atopic dermatitis. *Immunology and allergy clinics of North America* **30**, 309-321, doi:10.1016/j.iac.2010.05.001 (2010).

3 Eichenfield, L. F. *et al.* Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *Journal of the American Academy of Dermatology* **70**, 338-351, doi:10.1016/j.jaad.2013.10.010 (2014).

4 Brenninkmeijer, E. E., Schram, M. E., Leeflang, M. M., Bos, J. D. & Spuls, P. I. Diagnostic criteria for atopic dermatitis: a systematic review. *The British journal of dermatology* **158**, 754-765, doi:10.1111/j.1365-2133.2007.08412.x (2008).

5 Schneider, L. *et al.* Atopic dermatitis: a practice parameter update 2012. *The Journal of allergy and clinical immunology* **131**, 295-299 e291-227, doi:10.1016/j.jaci.2012.12.672 (2013).

6 Leung, D. Y. New insights into atopic dermatitis: role of skin barrier and immune dysregulation. *Allergology international : official journal of the Japanese Society of Allergology* **62**, 151-161, doi:10.2332/allergolint.13-RAI-0564 (2013).

7 Novak, N. & Leung, D. Y. Advances in atopic dermatitis. *Current opinion in immunology* **23**, 778-783, doi:10.1016/j.coi.2011.09.007 (2011).

8 Eichenfield, L. F. *et al.* Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *Journal of the American Academy of Dermatology* **71**, 116-132, doi:10.1016/j.jaad.2014.03.023 (2014).

9 NDA#020-934. Connetics February 1999.

10 Hengge UR, Ruzicak T, Schwartz RA, Cork MJ Adverse effects of Topical Glucocorticosteroids. J Am Acad Dermatology 2006 54:1 Continuing Medical Education.

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 Summary Basis of Approval LUXIQ® betamethasone 0.12% foam.

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13.0APPENDICES

APPENDIX A: Body Surface Area Calculation

Total Body Surface Area Calculation

To calculate the Total BSA the following procedure (Mosteller Formula[16]) should be followed.

Total Body Surface Area (BSA) in meters squared

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

It is preferable that the patient's height and weight be measured in cm and kg however if needed:

To convert inches (in) to centimeters (cm) the following conversion should be used
1 inch = 2.54 cm

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

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

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

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

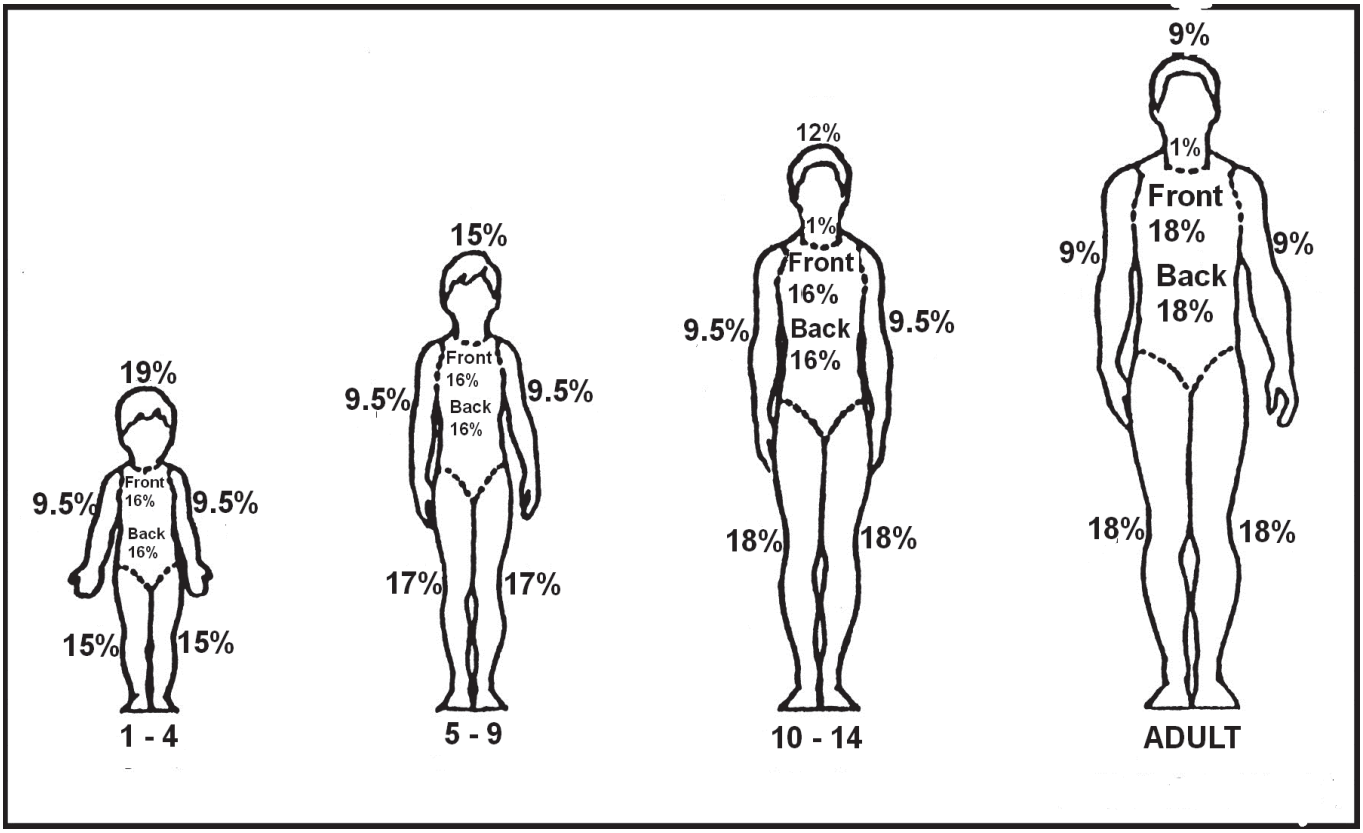
%BSA Affected

To estimate the % BSA Affected, the Investigator should use the method of approximation:

The "Rule of Nines" provides a general estimation of total BSA for several anatomic areas (each arm = 9%, each leg = 18%, back = 18%, chest and abdomen = 18%, head = 9%, groin = 1%). The Investigator may then visually estimate the proportion of the involved skin within each anatomic area and calculate the total percentage of BSA affected. In children, hips and legs are smaller and the head, neck and shoulders are larger, as a result, a modified "Rule of Nines" is used (see diagram below).

- 9% is taken from the legs and added to the head of a child < 1-year-old. For each subsequent year, 1% is returned to the legs until 9 years old at which time the head is in proportion to the adult
- By 9 years of age, the relative proportions assume the values for adult BSA and hence the adult diagram can be used as a reference at that time

Part	1-4 year child body % of total	5-9 year child body % of total	10-14 year child body % of total	15 year-adult body % of total
Arm	9.5%	9.5%	9.5%	9%
Head	19%	15%	12%	9%
Neck			1%	1%
Leg	15%	17%	18%	18%
Anterior trunk	16%	16%	16%	18%
Posterior trunk	16%	16%	16%	18%



APPENDIX B: Eczema Area and Severity Index Score (EASI)

The EASI is a composite score based on the severity of four different signs of atopic dermatitis in four different areas of the body multiplied by the percent of that specific body area affected multiplied by a weighting factor.

Erythema

0 = Clear	No evidence of erythema
1 = Mild	Definite light red coloration
2 = Moderate	Moderate redness, but not dark
3 = Severe	Dark red coloration

Induration/papulation/edema

0 = Clear	No evidence of any induration/papulation/edema
1 = Mild	Barely perceptible elevation
2 = Moderate	Clearly perceptible elevation
3 = Severe	Marked and extensive elevation

Lichenification

0 = Clear	No evidence of lichenification
1 = Mild	Slight thickening of skin discerible only by touch and with skin markings minimally exaggerated
2 = Moderate	Definite thickening of skin with skin marking exaggerated so that they form a visible criss-cross or ridged pattern
3 = Severe	Thickened skin with skin markings visibly portraying an exaggerated criss-cross or ridged pattern

Excoriation

0 = Clear	No evidence of excoriation
1 = Mild	Scant evidence of excoriation with no signs of deepers skin damage (absence of erosion or crusts)
2 = Moderate	Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust visible)
3 = Severe	Many erosive or crusty lesions present

The patient will be required to rate the severity of their pruritis (itching/scratching/discomfort) over the

previous 24 hours using the following scale:

Pruritis	
0 = None	None
1 = Mild	Occasional slight itching or scratching
2 = Moderate	Constant or intermittent itching/scratching/discomfort which is not disturbing sleep
3 = Severe	Bothersome itching/scratching/discomfort which is disturbing sleep

Eczema, induration, excoriation and lichenification are part of the EASI score but pruritis is not.

EASI Score

The EASI score is calculated as follows:
Head/neck (E + I + X + L) x Area x 0.1 (in children ages 0-7, x 0.2)
Upper Limbs (E + I + X + L) x Area x 0.2
Trunk (E + I + X + L) x Area x 0.3
Lower Limbs (E + I + X + L) x Area x 0.4 (in children ages 0-7, x 0.3)
EASI SCORE = SUM OF ABOVE 4 REGIONS

E: Erythema,
I: Induration/papulation/edema
X: Excoriation
L: Lichenification

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

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

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

EASI Score can be presented to the nearest whole number (no decimals and all numbers should be rounded, 0.5 should be rounded up to the nearest whole number)

The minimum score would be 0 and the Maximum Score would be 72. To be eligible for participation in this study a patient must have an EASI of at least 15 at baseline.

APPENDIX C: Investigator Global Assessment (IGA)

To be eligible for inclusion in the study the IGA must be 3 or 4 at baseline. To be considered a Clinical Success the patient must score a 0, 1 at Visit 3.

0	Clear	Minor, residual discoloration, no erythema or induration/papulation, no oozing/crusting
1	Almost Clear	Just perceptible erythema, with almost no induration/papulation and no oozing/crusting
2	Mild Disease	Definite pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate Disease	Red erythema with moderate induration/papulation and there may be some oozing/crusting
4	Severe Disease	Dark/bright red erythema with severe induration/papulation with oozing/crusting

APPENDIX D: Application Site Reactions

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

Burning

Erosion

Edema

Pain

Itching

Dryness

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

APPENDIX E: 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 3 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 3 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.

Visit 1 Test
A cortisol response test will be completed at Visit 1.

Visit 3 Test

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. As 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.

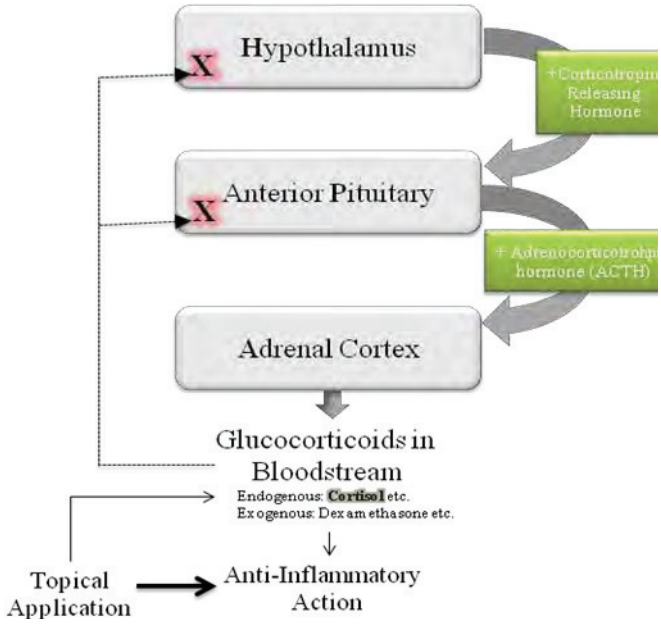
Patients should not be subjected to Cortrosyn™ testing, or any other challenge to their adrenal response, any sooner than 4 weeks from their last Cortrosyn™ test.

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

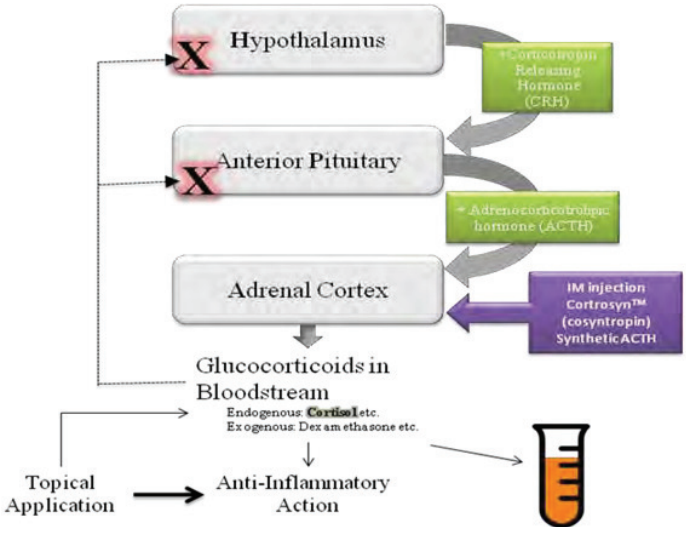
APPENDIX F: Evaluation of HPA Axis Suppression

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.

APPENDIX G: 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

APPENDIX H: 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.

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APPENDIX I: Investigator Brochure, Desoximetasone 0.15% Topical Spray

APPENDIX J: Protocol Revisions

Revision	Revision Number	Revision Date
• Protocol Rev date added to Title page, updated in the footer • Volume of blood draw updated in Appendix D • Clerical errors corrected throughout the document • Appendix H Protocol Revision added to the document	1	6/27/16

Revision	Revision Number	Revision Date
• Application Site Reactions (Appendix D) added to the protocol • Clerical corrections throughout the document • Protocol Revision Appendix J updated	2	9/06/16