CLINICAL STUDY PROTOCOL

A Randomized, Parallel Group, Open-Label, Multicenter Study to Assess the Potential for Adrenal Suppression and Systemic Drug Absorption Following Multiple Dosing with DFD-01 (betamethasone dipropionate) Spray, 0.05% in Adolescent Subjects with Moderate to Severe Plaque Psoriasis

Protocol Number: DFD01-CD-013 **Version:** 2
Phase: 3b **Date:** 13 March 2017

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CONFIDENTIAL

COMPLIANCE STATEMENT

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and ICH E6; 62 Federal Register 25691 (1997).

SIGNATURES

The signatures below provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator: **Site Number:** _____

Signature: _____ Date: _____

Name: _____
Title: _____
Address: _____
_____
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Signature: _____ Date: 27 Mar 2017

Srinivas Sidgiddi, MD
Director – Clinical Development, Dermatology

SYNOPSIS

Title: A Randomized, Parallel Group, Open Label, Multicenter Study to Assess the Potential for Adrenal Suppression and Systemic Drug Absorption Following Multiple Dosing with DFD-01 (betamethasone dipropionate) Spray 0.05% in Adolescent Subjects with Moderate to Severe Plaque Psoriasis

Sponsor:	Promius Pharma, LLC 107 College Road East Princeton, NJ 08540		
Study Centers:	8	**Number of Subjects:**	50
Study Period:	15 or 29 Days	**Clinical Phase:**	Phase 3b

Objectives:

The objectives of this study are:

- To evaluate the potential of DFD-01 (betamethasone dipropionate) Spray, 0.05% to suppress the hypothalamic-pituitary-adrenal (HPA) axis when applied twice daily for 15 days or when applied twice daily for 29 days, in adolescent subjects with moderate to severe plaque psoriasis under maximal use conditions with the final-to-be-marketed formulation.
- To assess the plasma concentrations of betamethasone dipropionate and its metabolites after multiple uses of DFD-01 (betamethasone dipropionate) Spray, 0.05%) under maximal use conditions with the final-to-be-marketed formulation.

Methods:

This is a 15 or 29-day, randomized, multicenter, multi-dose, open label study. Subjects, who are at least 12 years old and not more than 16.9 years old with moderate to severe plaque psoriasis, will be randomized to treatment with either DFD-01 spray 15-day treatment or DFD-01 spray 29-day treatment in a 1:1 ratio. These investigational products will be applied twice daily to all affected areas on the body excluding face, scalp, groin, axillae and other intertriginous areas. Subjects must have ≥ 10% body surface area (BSA) treated to achieve maximal use exposure.

Subject visits will take place at Screening, Baseline (Day 1), Day 8, Day 15, Day 29 (as appropriate) and Day 43 or 57 (if needed to confirm recovery). Clinical determinations of disease severity will be conducted using the Investigator Global Assessment (IGA) for overall severity at each visit. Subjects will be tested for HPA axis function using the ACTH stimulation test (a cosyntropin i.v. or i.m. injection) at the Screening Visit (at least 14 days and no more than 28 days prior to Baseline) and at the End of Treatment Visit (i.e., Day 15 for the 15-day treatment arm or Day 29 for the 29-day treatment arm). If HPA axis is suppressed at the End of Treatment Visit, another test will be administered approximately 28 days later (at Day 43 or 57, as appropriate) to confirm recovery. The ACTH stimulation test will be repeated approximately every 28 days until recovery is confirmed (or until the cause of suppression is diagnosed). Pre-stimulation and post-stimulation cortisol levels will be measured in serum and saliva.

At the time of the screening ACTH stimulation test, a PK blood sample will be taken to obtain a baseline value (PK screening sample). At the End of Treatment Visit, subjects will apply the last dose of study product at the clinic up to 60 minutes after a pre-treatment PK blood sample is taken (0 hour – End of Treatment Visit). PK blood samples will then be collected at 1, 3 and 6 hours (± 5 minutes) after application of the study product.

Local cutaneous safety evaluations (including atrophy, telangiectasia, pruritus, pain and burning/stinging) will be performed at Visits 2, 3, 4, and 5 (if appropriate). Other safety assessments include vital signs (blood pressure, pulse), urine pregnancy tests, and collection of adverse event data.

Number of Subjects:

A total of approximately 50 subjects will be randomized across approximately 8 sites in the United States. No more than 65 subjects will be randomized.

Diagnosis and Criteria for Inclusion / Exclusion:

Inclusion:

1. Subject and legal guardian understand the study procedures and agree to participate by giving written assent and written informed consent, respectively. Legal guardian must be willing to authorize use and disclosure of protected health information collected for the study.
2. Subjects must be at least 12 years of age and no more than 16.9 years of age at the time of randomization.
3. Subjects must weigh at least 55 pounds at the Screening Visit.
4. Subjects must present with a clinical diagnosis of stable (at least 3 months) plaque psoriasis.
5. Subjects with psoriasis involving ≥ 10% BSA, not including the face, scalp, groin, axillae and other intertriginous areas.
6. Subjects must have an IGA grade of at least 3 (moderate) at the Baseline Visit.
7. All females must complete a urine pregnancy test (test must have a sensitivity of at least 25 mIU/mL for human chorionic gonadotropin) at the Baseline Visit (Visit 2), and the test result must be negative to be eligible for randomization.
8. Female subjects who are sexually active must agree to use contraception during the study. Reliable methods of contraception are:
    - hormonal methods or intrauterine device in use ≥ 90 days prior to study product administration; or
    - barrier methods plus spermicide in use at least 14 days prior to study product administration.
    - partner has had a vasectomy at least 3 months previous to study product administration.

Note: Sexually inactive female subjects should be counseled to remain sexually inactive for the duration of the study and should be made to understand the possible risks involved in getting pregnant during the study. An abstinent female subject must agree that if she becomes sexually active during the study she will use an acceptable form of contraception.

9. Subjects must be in good general health as determined by the investigator and supported by the medical history and normal or not clinically significant abnormal vital signs (blood pressure and pulse).
10. Subjects whose results from the screening ACTH stimulation test are considered normal (blood cortisol level >18 ug/dL at 30 minutes post stimulation) and show no other signs of abnormal HPA axis function or adrenal response.

Exclusion:

1. Current diagnosis of unstable forms of psoriasis including guttate, erythrodermic, exfoliative or pustular psoriasis.
2. History of organ transplant requiring immunosuppression, HIV, or other immunocompromised state.
3. Have received treatment for any type of cancer within 5 years of the Baseline Visit.
4. Use within 60 days prior to the Baseline Visit of: 1) immunosuppressive drugs (e.g., tacrolimus, pimecrolimus), 2) systemic antipsoriatic treatment (e.g., methotrexate, cyclosporine, hydroxyurea), or 3) biologic treatment for psoriasis (e.g., infliximab, adalimumab, etanercept, ustekinumab, secukinumab, or alefacept).
5. Use within 30 days prior to the Baseline Visit of: 1) topical antipsoriatic drugs (salicylic acid, anthralin, coal tar, calcipotriene), 2) PUVA therapy, 3) systemic anti-inflammatory agents (e.g., mycophenolate mofetil, sulfasalazine, 6-thioguanine), or 4) UVB therapy.
6. Use within 30 days prior to the Screening Visit of any product containing corticosteroids. Inhaled, intraocular, intranasal, etc. steroids are <u>not</u> allowed.
7. Use within 14 days prior to the Baseline Visit of topical retinoids.
8. Subjects with known hypersensitivity to betamethasone dipropionate or any component of DFD-01.
9. Subjects who have an abnormal sleep schedule or work overnight.
10. Subjects who have participated in a study of an investigational product or device 60 days prior to the Baseline Visit.
11. Subjects unable to comply with study requirements.
12. Female subjects who are pregnant (or planning to become pregnant) or breast-feeding.
13. Subjects with a known history of acute adrenal crisis, Addison's disease or decreased adrenal output, low pituitary function or pituitary tumors.
14. Subjects who have a history of an adverse reaction to cosyntropin injection or similar test reagents.

15. Subjects with any history of illegal drug or alcohol use.

Investigational Product, Dose and Mode of Administration:

DFD-01 (betamethasone dipropionate) Spray, 0.05%

The investigational product will be applied topically to all affected areas (i.e., those areas that were affected at Baseline, even if resolved, and new lesions that develop at any time during the treatment period) twice daily, approximately 12 hours apart. The target dose is at least 3 to 5 g per day (10 to 15 pumps, twice daily). Product is not to be applied to face, scalp, groin, axillae, or other intertriginous areas.

Duration of Treatment and Study:

Subjects will treat affected areas for either 15 days or 29 days. Since the screening ACTH test must occur 14 to 28 days before the Baseline Visit, the total study duration is 29 to 43 or 43 to 57 days plus any wash-out period. Some subjects may need to return for a follow-up visit at Day 43 or 57.

Criteria for Evaluation:

Safety criteria:
The proportion of subjects with abnormal serum cortisol response for ACTH stimulation test at the end of treatment (cortisol serum level ≤18 ug/dL at 30 minutes post stimulation) is the primary safety variable.

Efficacy Criteria:
IGA will be collected and summary statistics provided.

Study Schedule (29-day treatment arm)

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screen[a]	Day 1 (Baseline)	Day 8[b]	Day 15[b]	Day 29[b] (End of Treatment)	Day 57[c]
Informed Consent	X					
Collect Demographic Data	X					
Inclusion and Exclusion Criteria	X	X				
Med History / Prior & Con Meds	X	X				
Vital Signs (BP, Pulse)	X	X	X	X	X	X
Urine Pregnancy Test	X[d]	X	X	X	X[d]	X[d]
Determine BSA	X	X			X	
IGA	X	X	X	X	X	
ACTH stimulation test[g] (blood and saliva samples)	X[e]				X[h]	X[i]
Local Cutaneous Safety Evaluation		X	X	X	X	
Randomization		X				
Weigh and Dispense Medication (as needed)		X	X	X		
Supervised treatment		X			X[k]	
Take Blood Samples for PK[j]	X				X	
Dispense/Review/Collect Study Diary		X	X	X	X	
Diagram affected areas to be treated		X	X	X		
Review Subject Instructions		X	X	X	X	
Collect and Weigh Used Containers			X	X	X	
Evaluate Compliance			X	X	X	
Review Concomitant Medications		X	X	X	X	X
Adverse Event Assessment		X[f]	X	X	X	X
End of Study					X	X

[a] No more than 60 days before Visit 2
[b] Allowed visit window ± 3 day
[c] If needed due to abnormal ACTH test result at End of Treatment Visit
[d] Pregnancy test just prior to ACTH stimulation test
[e] At least 14 days, and no more than 28 days, prior to Day 1
[f] Related to study procedures only
[g] ACTH stimulation test to be performed between 7:00 and 9:30AM
[h] ACTH stimulation test should be performed within 1 hour of time of when Screening test was performed
[i] ACTH stimulation test will be repeated until recovery (or is explained)
[j] Blood will be drawn at the time of the screening pre-stimulation ACTH test and at 0, 1, 3, 6 hours (+/-5 minutes) after application at End of Treatment Visit
[k] Weigh bottle before and after application

Study Schedule (15-day treatment arm)

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screen[a]	Day 1 (Baseline)	Day 8[b]	Day 15[b] (End of Treatment)	Day 43[c]
Informed Consent	X				
Collect Demographic Data	X				
Inclusion and Exclusion Criteria	X	X			
Med History / Prior & Con Meds	X	X			
Vital Signs (BP, Pulse)	X	X	X	X	X
Urine Pregnancy Test	X[d]	X	X	X[d]	X[d]
Determine BSA	X	X		X	
IGA	X	X	X	X	
ACTH stimulation test[g] (blood and saliva samples)	X[e]			X[h]	X[i]
Local Safety Evaluation		X	X	X	
Randomization		X			
Weigh and Dispense Medication (as needed)		X	X		
Supervised treatment		X		X[k]	
Take Blood Samples for PK[j]	X			X	
Dispense/Review/Collect Study Diary		X	X	X	
Diagram affected areas to be treated		X	X		
Review Subject Instructions		X	X	X	
Collect and Weigh Used Containers			X	X	
Evaluate Compliance			X	X	
Review Concomitant Medications		X	X	X	X
Adverse Event Assessment		X[f]	X	X	X
End of Study				X	X

[a] No more than 60 days before Visit 2
[b] Allowed visit window ± 3 day
[c] If needed due to abnormal ACTH test result at End of Treatment Visit
[d] Pregnancy test just prior to ACTH stimulation test
[e] At least 14 days, and no more than 28 days, prior to Day 1
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[g] ACTH stimulation test to be performed between 7:00 and 9:30AM
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[k] Weigh bottle before and after application

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List of Abbreviations

Abbreviations	Description
ACTH	Adrenocorticotropic hormone
AE	adverse event
BP	blood pressure
BSA	body surface area
CFR	Code of Federal Regulations
CRF	case report form
CRO	contract research organization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
i.m.	intramuscular
IRB	institutional review board
i.v.	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PHI	protected health information
PK	pharmacokinetics
SAE	serious adverse event
UPT	urine pregnancy test

List of Definitions

Term	Definition
Screening Visit (Visit 1)	The day a subject is screened according to the protocol inclusion/exclusion criteria, legal guardian having provided informed consent, and tentatively qualifies for randomization pending all screening activities or protocol required wash-out period.
Screened Subject	A subject who's legal guardian has signed informed consent and has completed part or all of the Screening Visit.
Baseline Visit (Visit 2/Day 1)	The day of randomization and the first study product application. The first study product application is done at the site by the subject during the visit.
Subject Number	A unique number assigned to a screened subject once informed consent is obtained. The number consists of the 3-digit unique site number followed by a 3-digit sequential number for each subject in chronological order (e.g., 406001, 406002, where the site number is 406 and the first and second screened subjects at site 406 are 001 and 002, respectively).
Randomized Subject	A subject is considered to be randomized once they have been assigned a study product per the randomization schedule.
Randomization Number	The number from the randomization schedule associated with the study product that is assigned to the subject at the time of study product dispensing.
Study product(s)	Investigational product(s)

1 INTRODUCTION

Promius Pharma, LLC has developed a new spray formulation of betamethasone dipropionate, DFD-01 - Betamethasone Dipropionate Spray, 0.05% (potency expressed as betamethasone), for the topical treatment of psoriasis. Betamethasone dipropionate is a synthetic, fluorinated corticosteroid.

Psoriasis is a multisystem disease with predominantly skin and joint manifestations. The major manifestation of psoriasis is inflammation of the skin characterized by disfiguring, scaling, and erythematous plaques that may be painful or pruritic. Psoriasis is a chronic disease that waxes and wanes during a patient's lifetime, is often modified by treatment initiation and cessation and has few spontaneous remissions (Menter, 2008).

Psoriasis affects 7.5 million or 2.2% of the USA population at an estimated cost of 11.25 billion dollars annually (National Psoriasis Foundation). The most common form of psoriasis is chronic plaque disease. This presents as well-defined red scaly plaques typically distributed over the scalp, lower back, and extensor aspects of the limbs. Clinical variants include guttate psoriasis, sebopsoriasis, and pustular forms of psoriasis. A minority of patients with psoriasis (7%) also develop a seronegative inflammatory arthritis. Microscopically, lesional skin shows increased proliferation and abnormal differentiation of keratinocytes, infiltration by activated T-helper lymphocytes and neutrophils, and activation of the cutaneous vasculature (Mendonca, 2003).

Approximately 80% of patients affected with psoriasis have mild to moderate disease. The majority of these patients can be treated with topical agents, which generally provide both good efficacy and safety. Topical agents are also used adjunctively for resistant lesions in patients with more extensive psoriasis who are being concurrently treated with either ultraviolet light or systemic medications. Treatment should be tailored to meet individual patient's needs. These needs vary depending on body location, characteristics of the psoriasis being treated including lesion thickness, degree of erythema, and amount of scaling, as well as patient preference. The choice of vehicle can alter the use and penetration of the medication (Menter, 2009).

There are many approved topical products containing betamethasone dipropionate on the market in the USA indicated for the treatment of corticosteroid responsive dermatoses such as psoriasis and atopic dermatitis. The first product was approved in 1975. Adverse events associated with the use of topical betamethasone dipropionate include erythema, folliculitis, pruritus, and vesiculation each occurring in less than 1% of patients.

In addition, the following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria.

DFD-01 contains 0.05% betamethasone dipropionate (potency expressed as betamethasone) in a convenient, cosmetically elegant spray formulation. The inactive ingredients are commonly

used excipients for topical products. More information about DFD-01 can be found in the Investigator's Brochure.

The current clinical study is intended to evaluate the potential for HPA axis suppression of this new formulation of betamethasone dipropionate in adolescent subjects with moderate to severe psoriasis. Exogenous corticosteroids can suppress the HPA axis, resulting in decreased circulating adrenocorticotropic hormone (ACTH) levels, atrophy of glucocorticoid-secreting cells in the adrenal cortex, and secondary adrenal insufficiency. HPA axis suppression will be determined from the results of an ACTH stimulation test.

The ACTH stimulation test measures how well the adrenal glands respond to the hormone ACTH. ACTH is a hormone produced in the pituitary gland that stimulates the adrenal glands to release cortisol. A normal response is a serum cortisol level of more than 18 ug/dL 30 minutes after the ACTH is injected. Cortisol can also be reliably measured in saliva (Gallagher, 2006) but the criteria for a normal response to ACTH has not been established. Both serum and saliva cortisol will be measured in this study to provide data about the saliva level criterion for a normal response.

The potential for HPA axis suppression of DFD-01 has been studied in adults with moderate to severe psoriasis (Study BDS1307). After 15 and 29 days of treatment, 20.8% (5 out of 24) and 0% (0 out of 24) of subjects had abnormal cortisol levels in the ACTH stimulation test, respectively. This study is to determine the potential for HPA axis suppression and extent of systemic drug exposure in the adolescent population with moderate to severe psoriasis.

2 ETHICAL CONSIDERATIONS

2.1 Institutional Review Board Review

The protocol, protocol amendments, subject recruiting materials, the informed consent form and any other materials provided to subjects must be approved by an Institutional Review Board operating in compliance with 21 CFR Part 56. A copy of the approval letter must be received by the sponsor or CRO prior to shipment of drug supplies to the site.

Records of the Institutional Review Board's review and approval of all documents pertaining to the study must be kept on file by the investigator and are subject to sponsor and FDA inspection at any time.

2.2 Ethical Conduct of Study

The investigator will ensure that this study is conducted in full conformity with the principles set forth in 21 CFR Part 50 – Protection of Human Subjects and in the Declaration of Helsinki (2013) (See Appendix 1).

2.3 Informed Consent

Written informed consent of subject's legal guardian must be obtained before a subject can participate in the study, prior to performing any study related procedures, and before withdrawal

of any therapies prohibited during the study. Subjects must provide written assent. Informed consent and assent is a process that is initiated prior to the subject's and legal guardian's agreement to participate in the study and continues throughout the subject's study participation. The process involves an extensive discussion with the subject and legal guardian about the study procedures and the risks and possible benefits of participation in the study.

2.4 Selection of Investigators

Investigators for the study should be board certified dermatologists licensed in the state where the study is being conducted, with knowledge and understanding of Good Clinical Practice (GCP) and experience in treating psoriasis. In some cases, qualified physicians who are not board certified dermatologists may participate based on training and experience in the treatment of psoriasis. Sub-investigators may be licensed physicians, physician assistants, or nurse practitioners with experience in psoriasis or dermatology and a good understanding of GCP. Investigators may delegate study tasks to other site personnel as long as they are qualified to perform the task and the delegation is documented.

3 STUDY OBJECTIVES

The objectives of this study are

- To evaluate the potential of DFD-01(betamethasone dipropionate) spray, 0.05% to suppress the hypothalamic-pituitary-adrenal (HPA) axis when applied twice daily for 15 days or when applied twice daily for 29 days in adolescent subjects with moderate to severe plaque psoriasis under maximal use conditions.
- To assess the plasma concentrations of betamethasone dipropionate and its metabolites after multiple uses of DFD-01 (betamethasone dipropionate) spray, 0.05% to DFD-01 under maximal use conditions in adolescent subjects with moderate to severe plaque psoriasis.

4 STUDY DESIGN

This is a 15 or 29-day, randomized, multicenter (approximately 8 sites), multi-dose, open label study. Approximately 50 adolescent subjects with moderate to severe plaque psoriasis will be randomized to treatment either with DFD-01 (betamethasone dipropionate) spray, 0.05% applied for 15 days or DFD-01(betamethasone dipropionate) spray, 0.05% applied for 29 days, in a 1:1 ratio. The investigational product will be applied twice daily to all affected areas on the body excluding face, scalp, groin, axillae and other intertriginous areas. Subject visits are scheduled at Screening, Baseline (Day 1) and Days 8, 15, 29 (as appropriate) and Day 43 or 57 (if needed). Clinical determinations of disease severity will be conducted using the Investigator Global Assessment (IGA) for overall severity at each visit.

Subjects will be tested for HPA axis function using the ACTH stimulation test at least 14 days and no more than 28 days, prior to the Baseline Visit and at the End of Treatment Visit. The screening ACTH stimulation test can be conducted on the day of the Screening Visit (if timing is appropriate) or on a separate day (e.g., when washout is needed). If HPA axis is suppressed at the End of Treatment Visit, another test will be administered at Day 43 or 57 (as appropriate)

to confirm recovery. The ACTH stimulation test will be repeated until the HPA axis is stabilized (or explained). Pre-stimulation and post-stimulation cortisol levels will be measured in serum and saliva.

At the time of the screening ACTH stimulation test, a blood sample for pharmacokinetics (PK) will be taken to obtain a baseline value (PK screening sample). At the End of Treatment Visit, subjects will apply the last dose of study product at the clinic up to 60 minutes after a pre-treatment PK blood sample is taken (0 hour – End of Treatment Visit). PK blood samples will then be collected at 1, 3 and 6 hours (± 5 minutes) after application of the study product.

Total blood sample volume taken at the Screening Visit will be approximately 16 mL and at the End of Treatment Visit approximately 34 mL. These blood volumes are safe for subjects who weigh at least 55 pounds and would not exceed approximately 2.5% of total blood volume.

Local cutaneous safety evaluations (including atrophy, telangiectasia, pruritus, pain and burning/stinging) will be performed at Visits 2, 3, 4 and 5 (if appropriate). Other safety assessments include vital signs (blood pressure, pulse), urine pregnancy tests, and collection of adverse event data.

5 SELECTION OF STUDY POPULATION

5.1 Number of Subjects

Approximately 50 subjects will be randomized. No more than 65 subjects will be randomized. There will be approximately 8 sites with each site randomizing 5 to 15 subjects.

5.2 Inclusion Criteria

1. Subject and legal guardian understand the study procedures and agree to participate by giving assent and written informed consent, respectively. Legal guardian must be willing to authorize use and disclosure of protected health information collected for the study.
2. Subjects must be at least 12 years of age and no more than 16.9 years of age at the time of randomization.
3. Subjects must weigh at least 55 pounds at the Screening Visit.
4. Subjects must present with a clinical diagnosis of stable (at least 3 months) plaque-type psoriasis.
5. Subjects with psoriasis involving $\geq$ 10% BSA affected, not including the face, scalp, groin, axillae and other intertriginous areas.
6. Subjects must have an IGA grade of at least 3 (moderate) at the Baseline Visit.
7. All females must complete a urine pregnancy test (test must have a sensitivity of at least 25 mIU/mL for human chorionic gonadotropin) at the Baseline Visit (Visit 2), and the test result must be negative to be eligible for randomization.
8. Female subjects who are sexually active must agree to use contraception during the study. Reliable methods of contraception are:

- hormonal methods or intrauterine device in use ≥ 90 days prior to study product administration; or
- barrier methods plus spermicide in use at least 14 days prior to study product administration.
- partner has had a vasectomy at least 3 months previous to study product administration.

Note: Sexually inactive female subjects should be counseled to remain sexually inactive for the duration of the study and should be made to understand the possible risks involved in getting pregnant during the study. An abstinent female subject must agree that if she becomes sexually active during the study she will use an acceptable form of contraception.

9. Subjects must be in good general health as determined by the investigator and supported by the medical history and normal or not clinically significant abnormal vital signs (blood pressure and pulse).
10. Subjects whose results from the screening ACTH stimulation test are considered normal (blood cortisol level >18 ug/dL at 30 minutes post stimulation) and show no other signs of abnormal HPA axis function or adrenal response.

5.3 Exclusion Criteria

1. Current diagnosis of unstable forms of psoriasis including guttate, erythrodermic, exfoliative or pustular psoriasis.
2. History of organ transplant requiring immunosuppression, HIV, or other immunocompromised state.
3. Have received treatment for any type of cancer within 5 years of the Baseline Visit.
4. Use within 60 days prior to the Baseline Visit of: 1) immunosuppressive drugs (e.g., tacrolimus, pimecrolimus), 2) systemic antipsoriatic treatment (e.g., methotrexate, cyclosporine, hydroxyurea), or 3) biologic treatment for psoriasis (e.g., infliximab, adalimumab, etanercept, ustekinumab, secukinumab, or alefacept).
5. Use within 30 days prior to the Baseline Visit of: 1) topical antipsoriatic drugs (salicylic acid, anthralin, coal tar, calcipotriene), 2) PUVA therapy, 3) systemic anti-inflammatory agents (e.g., mycophenolate mofetil, sulfasalazine, 6-thioguanine), or 4) UVB therapy.
6. Use within 30 days prior to the Screening Visit of any product containing corticosteroids. Inhaled, intraocular, intranasal, etc. steroids are not allowed.
7. Use within 14 days prior to the Baseline Visit of topical retinoids.
8. Subjects with known hypersensitivity to betamethasone dipropionate or any component of DFD-01.
9. Subjects who have an abnormal sleep schedule or work overnight.
10. Subjects who have participated in a study of an investigational product or device 60 days prior to the Baseline Visit.
11. Subjects unable to comply with study requirements.

12. Female subjects who are pregnant (or planning to become pregnant) or breast-feeding.
13. Subjects with a known history of acute adrenal crisis, Addison's disease or decreased adrenal output, low pituitary function or pituitary tumors.
14. Subjects who have a history of an adverse reaction to cosyntropin injection or similar test reagents.
15. Subjects with any history of illegal drug or alcohol use.

Subjects must not use the medications shown in Table 1 for the period specified before the Baseline Visit (Visit 2).

Table 1: Wash-out Table

Product	Prior to ACTH stimulation test	Prior to Baseline Visit 2
Other investigational product or device Immunosuppressive drugs (tacrolimus or pimecrolimus) Systemic antipsoriatic agents (methotrexate, cyclosporine, hydroxyurea) Biologic treatment for psoriasis (infliximab, adalimumab, etanercept, ustekinumab, secukinumab, or alefacept).		60 days
Systemic anti-inflammatory agents (mycophenolate mofetil, sulfasalazine, 6-thioguanine) PUVA therapy UVB therapy Topical antipsoriatic drugs (salicylic acid, anthralin, coal tar, calcipotriene)		30 days
Any product containing corticosteroids	30 days	
Topical retinoids		14 days

6 SUBJECT TREATMENT

6.1 Investigational Products

6.1.1 Description

The investigational product is:

- DFD-01 (betamethasone dipropionate) spray, 0.05%
  (120 mL spray bottle, Promius Pharma, LLC)

DFD-01 Spray will be provided by Promius Pharma, LLC, Princeton, NJ 08540. The spray formulation is a thin, white emulsion.

Initially, 6 bottles (DFD-01 Spray 0.05%) will be sent to each site. Additional bottles will be sent as needed. The spray product should be shaken before use.

6.1.2 Labels and Packing

Bottles will be packed one to a box. Labels on the bottles will be in English and Spanish and include product name, protocol number, a unique bottle number, investigational use warning, storage conditions, brief instructions for use, and sponsor name and address. Subjects will be asked to return bottles in the box.

Bottle Label for DFD-01 Spray - Provided in English and Spanish Text

DFD-01

Protocol: DFD01-CD-013 Bottle ID: FXXXX

Store at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). For Topical Use Only. Shake well before use. Apply twice daily as instructed. Rub in gently and completely.
Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use

Promius Pharma, LLC
Princeton, NJ 08540

Labels on the box will be in English and Spanish and include product name, protocol number, a unique bottle number, investigational use warning, and storage conditions, brief instructions for use, and sponsor name and address. In addition, there will be a place to write the subject number and subject initials. The box-label will also have a tear-off panel that includes the protocol number and unique bottle number. The tear-off panel is to be affixed to the source document (drug dispensing record).

Box Label for DFD-01 Spray - Provided in English and Spanish Text

DFD-01 Protocol: DFD01-CD-013 Bottle ID: FXXXX Subject No.: _____ Subject Initials: _____ Store at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). For Topical Use Only. Shake well before use. Apply twice daily as instructed. Rub in gently and completely. Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use. Promius Pharma, LLC, Princeton, NJ 08540	DFD-01 Protocol: DFD01-CD-013 Bottle ID: FXXXX Subject No.: _____ Subject Initials: ____ *Tear off portion to be affixed to source document and filed with dispensing confirmation in Subject's chart.*

6.1.3 Accountability

Documentation of receipt, study product inventory, and return shipments of the study product must be maintained at each study site. Upon receipt of the study product supplies, an inventory must be performed. It is important that site personnel count and verify that the shipment contains all the items noted in the shipment record and that they are in good condition. At study completion, all containers of study product, used and unused, must be returned to the sponsor or designee.

In addition, a study product accountability log showing dispensing to and return by subjects must be maintained at each study site. Any dispensed bottles that are not returned to the clinic must be documented on the log.

6.1.4 Dispensing and Return

One bottle of study product will be dispensed to subjects at the Baseline Visit (Visit 2) by study staff. The weight of the bottles should be recorded before dispensing. Additional bottles will be dispensed as needed. Partially filled bottles can be redispensed back to the subject. The study product to be dispensed for each subject will be identified by referring to the site randomization schedule. The tear-off panel is to be affixed to the source document. Subject initials and subject number must be written on the box label. Study staff will then dispense and instruct subject and legal guardian on study product use.

Dispensing and return of study product must be documented on the Investigational Product Site Dispensing and Return Log.

Subjects must return the used bottles even if empty throughout the trial. At the end of the trial, all used and unused bottles must be returned to the clinic for eventual destruction by the sponsor or designee. Any dispensed bottles that are not returned to the clinic must be documented on the log.

6.1.5 Storage

Study products must be kept in a secure room temperature-controlled/monitored space at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F).

6.2 Treatment Regimen

Subjects will use study product under the supervision and with help, if needed, of their legal guardian, twice daily with approximately 12 hours between applications for either 15 or 29 days starting on Day 1 during the study visit. Subjects will apply study product to all affected areas except the face, scalp, groin, axillae and other intertriginous areas. The target dose is at least 3 to 5 g per day (10 to 15 pumps of spray) , twice daily, applied at approximately 2 mg/cm^2 on 10% BSA – 1500 cm^2). Subjects with greater than 10% BSA will apply more, as appropriate. All baseline affected areas and newly affected areas should be treated until the end of the study even if cleared. The investigator shall diagram the affected areas (in the source document), update the diagram at each visit, and remind the subjects and legal guardians where study product is to be applied at each visit using the diagram. Study product should be sprayed directly onto affected areas and rubbed in gently and completely. Study product should be applied after bathing, if applicable.

The first and last dates of treatment should be recorded in the CRF with the number of applications made on those days.

The first and last application of study product will be applied by the subjects or their legal guardian at the site under supervision. At the last visit, the bottle should be weighed before and after the application to determine the amount of study product applied for the last dose.

6.3 Treatment and Protocol Compliance

Subjects and legal guardians will be provided an instruction sheet specific for the study product, along with a diagram of affected areas to be treated. Study staff should review the instruction sheet and diagram with the subjects and their legal guardian to ensure protocol compliance. If new affected areas appear between visits, the subject may start treating the new area between visits. Treatment areas are to be updated on the diagram at each visit.

At each visit, the investigator or designee will interview subjects and their legal guardian concerning treatment compliance and ask if any doses have been missed. The investigator will also ask about compliance with protocol requirements. Protocol deviations will be recorded in the subject's chart and Protocol Deviation Form. A Protocol Deviation Form is not needed for

missed visits, missed applications, out-of-window visits and missing data. These items will be apparent from the missing data on the CRF and will be identified programmatically during data analysis for purposes of reporting. The sponsor should be consulted before discontinuing subjects due to protocol deviations unless safety is a concern.

Subjects/legal guardian will be provided a diary card for documenting the dates of applications. The subjects and legal guardian will review the diary card with the investigator or designee at each visit. The number of applications and the number of missed applications will be recorded on the CRF. By definition, there are no missed applications after the last date of treatment even if recorded on the diary.

In addition, bottles of study product will be weighed before dispensing and before and after the last application. These weights should be entered into the CRF.

6.4 Method of Assigning Subjects to Treatment Groups

Approximately 50 subjects will be assigned randomly to one of the two treatment groups in a 1:1 ratio (25 for DFD-01 spray 29-day and 25 for DFD-01 spray 15-day). A subject randomization schedule will be created stratified by site. The site randomization schedule will be provided to each site for reference during randomization and drug dispensing. The next available randomization number and associated treatment duration will be assigned to subjects eligible for randomization at the time of study product dispensing in sequential order (e.g. the first subject to be dispensed study product for the first time on any particular day will be assigned the next available randomization number and study duration). No randomization number is to be skipped. The date and time of randomization, the randomization number and the assigned study product should be entered on the CRF. The randomization schedule will be generated and maintained by a third party vendor.

The investigator shall ensure that study products are only used by subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator and in accordance with the protocol.

6.5 Blinding

6.5.1 Method of Blinding

This is an open label study.

6.5.2 Unblinding

This is an open label study; therefore, there is no unblinding involved.

6.6 Prior and Concomitant Therapy

Chronic medications being used at the time of the Screening and Baseline Visit, with the exception of those specified as prohibited, may be continued at the discretion of the Investigator. History of medications, therapies and procedures are collected from the prior 2 month period for determination of eligibility.

New medications or the change in a dose of a current medication, required for another medical condition, which in the opinion of the investigator will have no material impact on the study, are permitted. The addition of such a new medication during the study will be documented as a concomitant medication and the associated medical need must be recorded as an adverse event.

All medications (topical, oral, prescription, over-the-counter, and herbal medications) and medical therapies or procedures that are used during the study for other diseases/conditions must be recorded on the CRF. Medications taken before the Baseline Visit need not be recorded on the CRF but should be reviewed to determine eligibility.

The following medications are prohibited during the study:

- inhaled, intraocular, intranasal steroids, etc
- systemic steroids
- systemic antipsoriatics (methotrexate, cyclosporine, hydroxyurea)
- PUVA therapy
- UVB therapy
- topical antipsoriatic drugs (salicylic acid, anthralin, coal tar, calcipotriene)
- topical corticosteroids
- immunosuppressive drugs (tacrolimus, pimecrolimus)
- topical retinoids (tazarotene, tretinoin)
- systemic anti-inflammatory drugs (mycophenolate mofetil, sulfasalazine, 6-thioguanine)
- biologics (infliximab, adalimumab, etanercept, ustekinumab, secukinumab or alefacept)
- oral retinoids (acitretin, isotretinoin)

The use of illegal drugs or prescription drugs that have not been prescribed for the subject are not permitted during the study.

Topical products other than the assigned treatment including moisturizers, creams, ointments, lotions, and powders applied on or near the affected areas that are being treated with study product should not be used during the study from Baseline Visit to End of Treatment Visit. Moisturizers can be used on the face, scalp, groin, axillae and other intertriginous areas. If a subject has been regularly using an anti-psoriasis, medicated shampoo product (e.g., tar shampoo, salicylic acid shampoo, zinc pyrithione) on the scalp for 3 months prior to randomization, he/she may continue on the same. Subjects with scalp psoriasis may not start the use or change the use of an anti-psoriasis, medicated shampoo product for the scalp during the study.

Use of the following should not occur during the study:

- tanning booths, sun lamps, or nonprescription UV light sources
- phototherapy
- sunbathing
- occlusive dressings on treated areas

If HPA axis suppression test is abnormal at the End of Treatment Visit, subjects should be advised to avoid products containing corticosteroids until recovery is determined.

7 STUDY PROCEDURES AND EVALUATIONS

7.1 Informed Consent Process

Informed consent must be obtained from the subject's legal guardian before a subject can participate in the study, prior to performing any study related procedures and before withdrawal of any therapies prohibited during the study. The investigator must discuss the study fully with the subject and the legal guardian. Subjects must demonstrate their willingness to participate in the study and comply with the study procedures by giving written assent. The consent form must be signed and dated by the subject's legal guardian. A copy of the consent form and assent form must be given to the legal guardian and subject, and the date of the consent process and who conducted the consent process must be documented in the source documents.

7.2 Screening

The Screening Visit should occur no more than 60 days before the Baseline Visit.

The screening ACTH stimulation test must be conducted at least 14 days and no more than 28 days prior to the Baseline Visit. Subjects should tentatively qualify for study enrollment before the ACTH stimulation test is conducted. The ACTH stimulation test can be conducted on the day of the Screening Visit (if timing is appropriate) or on a separate day (e.g., when washout is needed).

The subject's medical history should be recorded in the source documents and reviewed for study eligibility. However, only the concurrent medical conditions need to be entered on the CRF.

A screen failure is a subject who received information about the study, including signing an assent/consent form, and possibly performing some study related procedures but was not randomized. The subject number, date of visit, date of consent, reason for screen failure, and study status (screen failure) will be captured on the CRF for every screen failure subject.

7.3 Demographic and Baseline Characteristics

Demographic variables include age (computed from date of birth and Baseline Visit date), race, ethnicity, weight and sex. Baseline characteristics are the baseline values for ACTH stimulation test, IGA and BSA affected (body surface area affected excluding the face, scalp, groin, axillae and other intertriginous areas). BSA should be determined using the area of the subject's hand print (palm plus extended fingers) as an estimate of 1% BSA (Finlay, 2005).

7.4 Efficacy Assessments

7.4.1 Investigator's Global Assessment (IGA)

Clinical determinations of disease severity using IGA will be performed at each visit from screening through the end of treatment. The IGA scoring is shown in Table 2 below. IGA score

is a static assessment of disease severity and should be based on overall severity of signs at the visit. The inclusion criteria for this study require a Baseline IGA of at least 3 (moderate).

Table 2: Investigator's Global Assessment (IGA) of Disease Severity

Score	Grade	Definition
0	None	No plaque elevation above normal skin level may have residual non-erythematous discoloration no psoriatic scale no erythema
1	Minimal or Almost clear	No more than: very slight elevation above normal skin level faint light pink coloration occasional very fine scale partially covering some of the lesions
2	Mild	No more than: slight but definite elevation of plaque above normal skin level light red coloration fine scale with some lesions partially covered
3	Moderate	No more than: definite elevation with rounded or sloped edges to plaque definite red coloration somewhat coarse scale with most lesions partially covered
4	Severe/ Very Severe	At least one: marked elevation with hard, sharp edges to plaque dark red coloration coarse, thick scale with virtually all lesions mostly covered and a rough surface

7.4.2 BSA

BSA affected should be determined at the Screening, Baseline and End of Treatment Visits. BSA should be determined using the area of the subject's hand print (palm plus extended fingers) as an estimate of 1% BSA (Finlay, 2005).

7.5 Safety Assessments

7.5.1 ACTH Stimulation Test

Subjects will be tested for HPA axis function using the ACTH stimulation test (cosyntropin i.v. or i.m. injection) at a Screening Visit and at the End of Treatment Visit. If HPA axis is suppressed at the end of treatment, another test will be administered 28 days later (at approximately Day 43 or 57, as appropriate) to confirm recovery. The ACTH stimulation test will be repeated approximately every 28 days until recovery is confirmed or until the cause of suppression is diagnosed. The test should be conducted between the hours of 7:00 and 9:30 AM. The Screening Visit test must be normal to be eligible for the study (cortisol level > 18 ug/dL at 30 minutes post stimulation). The End of Treatment test should be performed within 1 hour of the time when the Screening Visit test was performed.

For female subjects, a urine pregnancy test will be conducted *just prior* to the ACTH stimulation test. The test must have a sensitivity of at least 25 mIU/mL for human chorionic gonadotropin. The test must be negative to be eligible for the study.

Procedure
The entire test must be completed between approximately 7:00 am and 9:30 am, including pre- and post-stimulation blood and saliva samples. A pre-dose, control blood sample of 4 to 5 mL will be collected in a serum separator tube and a pre-dose, control saliva sample of 0.2 mL to 0.5 mL will be collected with a Salivette® collection system. Then 0.25 mg of cosyntropin, reconstituted according to package insert instructions, will be injected intravenously or intramuscularly. The chosen route should be recorded on the CRF. The reconstituted drug product should be inspected visually for particulate matter and discoloration prior to injection. Reconstituted cosyntropin should not be retained. A second blood sample of 4 to 5 mL and a second saliva sample of 0.2 mL to 0.5 mL will be collected 30 minutes after injection of cosyntropin. Both blood sampling and cosyntropin administration (if administered intravenously) should take place in the same arm, if possible.

Sample Preparation and Shipment
All blood samples for estimation of serum cortisol levels should be centrifuged, serum separated and stored frozen (-20° C) until shipped according to the laboratory manual. Saliva samples should be stored frozen (-20° C) until shipped according to the laboratory manual.

Sample Analysis
The determination of the serum and saliva cortisol levels will be estimated by a validated method. A normal response is defined as a serum cortisol level of more than 18 ug/dL at 30 minutes post-stimulation. An abnormal response at end of treatment should be recorded as an adverse event of HPA axis suppression.

7.5.2 Other Safety Assessments

Other safety assessments include vital signs, local cutaneous safety evaluation of the treated skin, and adverse events (AEs). Vital signs (blood pressure, pulse) will be collected at each visit. Adverse events will be collected by spontaneous reports from subjects and legal guardian, either verbal or recorded in the subject diary, by directed questioning of subjects and legal guardian, and by observation (see Section 8 for details about AEs).

At Visits 2 (Baseline) through the End of Treatment Visit, the investigator will assess local cutaneous safety by examining treated areas for clinically significant atrophy and telangiectasia that will be recorded on the CRF as present or absent. The investigator will also ask the subject if any burning/stinging, pain, or itching has occurred in the treated areas since the last visit (for Visit 2 in the last 2 weeks). Baseline assessments are made prior to first application. Subsequent to the Baseline Visit, for each symptom reported by subjects and/or each clinically significant sign, the presence of the sign or symptom must be recorded as "Yes" even if severity is not worse than Baseline. An adverse event should be recorded if the severity is worse than Baseline.

For female subjects, urine pregnancy tests will be conducted at Screening, Baseline, and every subsequent visit. These tests will be conducted just prior to the ACTH stimulation test, as

appropriate. The test must have a sensitivity of at least 25 mIU/mL for human chorionic gonadotropin.

Adverse events, whether believed by the investigator to be related or unrelated to treatment, will be recorded on the CRF.

7.5.3 Drug Concentration Measurements/PK Blood Sampling

Sampling Schedule
A screening PK blood sample will be taken at the time of the screening ACTH stimulation test to obtain a baseline value.

At the End of Treatment Visit, subjects will apply the last dose of study product at the clinic up to 60 minutes after a pre-treatment PK blood sample is taken (0 hour – End of Treatment Visit). PK blood samples will then be collected at 1, 3 and 6 hours (± 5 minutes) after application of the study product.

Each blood draw will be accomplished by a fresh, clean venipuncture or collection from previously implanted catheter. Blood (approximately 6 ml per PK time point) will be collected in NaF/Na2EDTA blood collection tubes. Approximately a total of 30 mL of blood per subject will be drawn for drug assays during the study (6 mL at the Screening Visit and 24 mL at the End of Treatment Visit).

Sample Processing
Within approximately 1 hour of collection, plasma should be separated and processed. Samples should be stored and shipped according to the laboratory manual.

Analytical Procedure
Plasma betamethasone, betamethasone-17-propionate, and betamethasone -17,21-dipropionate will be measured by a validated, LC/MS/MS analytical method with a limit of quantitation of at most 5 pg/mL. Each assay run should include standards and quality control samples. The reference standard should be obtained from an official source. Failed batches will be documented in a run summary.

A validation report describing the method accuracy, precision, linearity, and robustness must be available for the analytical procedure. Stability of analytes must be shown for the storage period before assay and during the assay procedures.

7.6 Early Withdrawal of Subjects

1. Subjects should be withdrawn from the study if they or their legal guardian no longer wish to participate, are being uncooperative, or if the investigator feels that it is in the best interest of the subject to withdraw.
2. Subjects with protocol deviations or for whom it is discovered should have been excluded should not be withdrawn unless there is a safety concern. The protocol deviation should be recorded in the subject's chart and Sponsor Consultation form.

3. Subjects who experience an AE resulting in or requiring discontinuation of study product use should be encouraged, in conjunction with their legal guardian, to be followed until the AE is resolved or stabilized.
4. If a female subject becomes pregnant during the study, study product will be discontinued immediately and she will be followed through the pregnancy and delivery. Details of the pregnancy, delivery and health of the infant should be recorded on the Pregnancy Surveillance Form and the sponsor notified immediately.
5. At the time of study discontinuation, the investigator will record the reason for early withdrawal, date of last study product application, date of last visit or contact, collect adverse event data, and, if possible, perform all End of Treatment Visit specific evaluations. Every attempt should be made to contact subjects who are lost-to-follow-up via their legal guardian for a final safety assessment. At least three attempts must be documented in the subject's chart including the use of at least 1 certified letter. Any contact, either direct or indirect, should be made with the purpose to document the final status of the subject with regard to safety.
6. Subjects who withdraw early will not be replaced.

7.7 Modification of Protocol

No amendments to this protocol can be made without consultation with and agreement of the sponsor, the FDA, and IRB. Amendments must be made in writing. Modifications needed for the safety of subjects will be made immediately with notifications made as soon as possible.

7.8 Early Termination of Study

If it is determined by the sponsor or investigators that the study presents an unreasonable and significant risk to subjects, the study will be terminated as soon as possible, and in no event later than 5 working days following the determination that the study should be discontinued. The IRB and FDA must be notified as soon as possible about early termination of the study due to safety concerns.

7.9 Study Schedule

Study Schedule charts can be found on pages 7 and 8. There are at least 4 or 5 study visits; Screening (Visit 1), Baseline (Visit 2, Day 1), Day 8 (Visit 3), Day 15 (Visit 4 – End of Treatment Visit for the 15-day treatment group), and Day 29 (Visit 5 – End of Treatment Visit for the 29-day treatment group). A supplemental Visit 5 or 6 (Day 43 or 57) may be required to repeat the ACTH stimulation test if it was abnormal at the End of Treatment Visit.

This is a short trial and it is imperative that subjects and their legal guardians understand the importance of attending each visit as scheduled. This should be discussed with the subject and legal guardian before randomization at Visit 2. Randomized subjects and legal guardians must be counseled to keep all scheduled appointments and to return to the site within the permitted visit windows for each treatment visit (± 3 days for Visits). If a subject misses a visit, they and their legal guardians, should be encouraged to attend the next visit scheduled from the Baseline

Visit (Visit 2) date. It is especially important for the subject to complete the End of Treatment evaluation.

7.9.1 Visit 1 - Screening Visit (60 days or less from Baseline Visit 2)

1. Obtain written informed consent from legal guardian and written assent from subject prior to completing any study procedures. Document informed consent and assent in the subject's study record.
2. List subject on Screening/Enrollment Log. Assign subject number consisting of the 3 digit site number followed by sequential 3 digit numbers starting with 001 (e.g. 400001, 400002, 400003, etc.).
3. Collect demographic data – date of birth, sex, race, weight, and ethnicity.
4. Review and record medical history and concomitant medications, therapies and procedures. Medical history should be collected for the prior 1 year period and concomitant medications, therapies and procedures collected from the prior 2 month period. (record on source only)
5. Screen subject according to the study inclusion/exclusion criteria to determine tentative eligibility.
6. Initiate any protocol required washout.
7. Assess severity of psoriasis using IGA (record on source only).
8. Assess BSA excluding face, scalp, axillae, groin and other intertriginous areas. (record on source only)
9. Collect vital signs (blood pressure, pulse). (record on source only)
10. Conduct urine pregnancy test (UPT) for all female subjects (record on source only). Test must be negative to proceed.
11. If tentatively eligible and UPT is negative, conduct ACTH stimulation test (approximately 10 mL of blood is required). This test should be conducted at least 14 days and no more than 28 days prior to Visit 2 (Baseline). The entire test, including pre- and post-stimulation blood and saliva samples, should be completed between approximately 7:00 am and 9:30 am. Schedule for another day if needed. Also a screening PK blood sample will be drawn to obtain a baseline value. Blood (approximately 6 ml) will be collected in NaF/Na2EDTA blood collection tubes for PK analysis.

    Note: Subjects with an abnormal ACTH stimulation test (cortisol level $\leq$ 18 ug/dL at 30 minutes post stimulation) should be referred to their primary care physician, as needed.

7.9.2 Visit 2 - Day 1 - Baseline Visit

1. Update the medical history and concomitant medications. Any medical event (not related to a protocol intervention) that occurred since informed consent was signed should be recorded as medical history if still ongoing.
2. Collect adverse events. Any new medical event, need for new medication, or change in medication dosing caused by a protocol procedure performed at the Screening Visit should

be considered an adverse event except for worsening of psoriasis.

3. Confirm eligibility according to inclusion/exclusion criteria.
4. Conduct urine pregnancy test on female subjects. Record method of contraception, as applicable, on source only.
5. Collect vital signs (blood pressure, pulse).
6. Conduct clinical assessments:
   a. IGA (Table 2)
   b. Local cutaneous safety evaluation for clinically significant atrophy and telangiectasia in areas to be treated. The investigator should also ask the subject if any burning/stinging, pain, or itching has occurred in the areas to be treated in the last 14 days.
   c. Diagram affected areas to be treated (excluding face, scalp, axillae, groin and other intertriginous areas).
   d. Determine BSA excluding face, scalp, axillae, groin and other intertriginous areas.
7. Randomize the subject by referring to the randomization schedule and dispense study product to the subject/legal guardian. The tear-off panel from the box is to be affixed to the source document. Make a note on source document regarding treatment duration.
8. Instruct subject and legal guardian on study product use. Review the appropriate Subject Instructions with subject (See Appendix 2). Using the diagram of affected areas, have the subject treat the affected areas under supervision after weighing the study product.
9. Dispense and review use of diary. Remind subject and legal guardian to record actual application dates and/or potential adverse events as well as any medication used in the diary and to bring diary to each visit.
10. Schedule next visit.
11. Complete CRF for all subjects including screen failures. Only enter concurrent medical conditions and concomitant medications on the CRF.

7.9.3 Visit 3 - Day 8 ± 3 days

1. Evaluate treatment and protocol compliance and record any deviations. This includes a review of the diary card for number of applications and missed applications.
2. Conduct clinical assessments:
   a. IGA (Table 2)
   b. Local cutaneous safety evaluation for clinically significant atrophy and telangiectasia in the treated areas. The investigator should also ask the subject and legal guardian if any burning/stinging, pain, or itching has occurred in the treated areas since the last visit.
   c. Update diagram of affected areas to be treated. Subjects should continue to treat areas that have cleared and any new areas that develop during the treatment period.
3. Collect vital signs (blood pressure, pulse).

4. Conduct urine pregnancy test for female subjects. Test must be negative to proceed.
5. Collect adverse event data. This includes a review of the diary card for potential AEs.
6. Update concomitant medications data.
7. Redispense diary and review instructions and diagram of affected areas to be treated with subject.
8. If subject requires more study product, weigh then dispense the assigned study product, as needed. Collect and record weight of empty or nearly empty bottles. Re-dispense partially filled bottles.
9. Schedule next visit. Remind the subject to come to the next visit well hydrated.
10. Complete CRF.

7.9.4 Visit 4 - Day 15 ± 3 days (29-day treatment group only; not applicable for 15-day treatment group)

1. Evaluate treatment and protocol compliance and record any deviations. This includes a review of the diary card for number of applications and missed applications.
2. Conduct clinical assessments:
   a. IGA (Table 2)
   b. Local cutaneous safety evaluation for clinically significant atrophy and telangiectasia in the treated areas. The investigator should also ask the subject and legal guardian if any burning/stinging, pain, or itching has occurred in the treated areas since the last visit.
   c. Update diagram of affected areas to be treated. Subjects should continue to treat areas that have cleared.
3. Collect vital signs (blood pressure, pulse).
4. Collect adverse event data. This includes a review of the diary card for potential AEs.
5. Update concomitant medications data.
6. Conduct a urine pregnancy test for female subjects. The test must be negative for the subject to continue in the study.
7. Redispense diary and review instructions and diagram of affected areas to be treated with subject.
8. If subject requires more study product, weigh then dispense assigned study product, as needed. Collect and record weight of empty or nearly empty bottles. Re-dispense partially filled bottles.
9. Schedule next visit. Remind subject to come to the next visit well hydrated.
10. Complete CRF.

7.9.5 Visit 4 (Day 15 ± 3 days) for 15-day treatment group or Visit 5 (Day 29 ± 3 days) for 29-day treatment group (End of Treatment Visit 7:00 am to 9:30 am)

1. Evaluate treatment and protocol compliance and record any deviations. This includes a review of the diary card for number of applications and missed applications.
2. Conduct clinical assessments:
   a. IGA (Table 2)
   b. Local cutaneous safety evaluation for clinically significant atrophy and telangiectasia in the treated areas. The investigator should also ask the subject if any burning/stinging, pain, or itching has occurred in the treated areas since the last visit.
   c. Assess BSA excluding face, scalp, axillae, groin and other intertriginous areas.
3. Collect vital signs (blood pressure, pulse).
4. Collect adverse event data. This includes a review of the diary card for potential AEs.
5. Update concomitant medications data.
6. Conduct urine pregnancy test for female subjects. Test must be negative to proceed with the ACTH stimulation test.
7. Draw pre-treatment (0 hour) PK blood sample no more than 60 minutes before planned study product application and process sample. Blood (approximately 6 ml) will be collected in NaF/Na2EDTA blood collection tubes.
8. Collect all study product bottles and record weight.
9. Supervise last application of study product by subject. Record weight of bottle after application.
10. Draw post-treatment PK blood samples at 1, 3 and 6 hours after study product application and process samples. Blood (approximately 6 ml each sample for a total of 18 mL) will be collected in NaF/Na2EDTA blood collection tubes.
11. Conduct ACTH stimulation test after the last application (approximately 5 mL for each sample for a total of 10 mL). The entire test, including pre- and post-stimulation blood and saliva samples, should be completed between approximately 7:00 am and 9:30 am and within one hour of the time of the screening ACTH stimulation test.
12. Collect study diary.
13. Complete CRF.

7.9.6 Visit 5 (Day 43) or 6 (57) (if required)

If HPA axis is suppressed at End of Treatment Visit, another test will be administered at approximately Day 43 (for 15-day treatment groups) or Day 57 (for 29-day treatment group) to confirm recovery. The ACTH stimulation test will be repeated approximately every 28 days until HPA axis is stabilized (or explained).

1. Collect vital signs (blood pressure, pulse).

2. Perform urine pregnancy test for female subjects. Test must be negative to proceed with the ACTH stimulation test.
3. Conduct ACTH stimulation test. The entire test, including pre- and post-stimulation blood and saliva samples, should be completed between approximately 7:00 am and 9:30 am.
4. Collect adverse event data.
5. Update concomitant medications data.
6. Complete CRF.

8 ADVERSE EVENTS

Adverse events will be collected by spontaneous reports from subjects and legal guardians, either verbal or recorded in the subject diary, by directed questioning of subjects, and by observation.

Adverse events associated with the use of topical betamethasone dipropionate include erythema, folliculitis, pruritus, and vesiculation each occurring in less than 1% of patients.

In addition, the following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria.

The investigator is to pay special attention at each post-treatment visit to any signs of clinically significant atrophy or telangiectasia and report presence as an adverse event if severity is worse than baseline. The investigator will also ask the subject if any burning/stinging, pain, or itching has occurred in the treated areas since the last visit (for Visit 2 in the last 14 days). Baseline assessments are made prior to first application. Subsequent to the Baseline Visit, for each symptom reported by subjects and/or each clinically significant sign, the presence of the sign or symptom must be recorded as "Yes" even if severity is not worse than Baseline. An adverse event should be recorded if the severity is worse than Baseline.

An adverse event is any untoward medical occurrence in a subject participating in a clinical trial. The event does not necessarily have to have a causal relationship with the study product. An adverse event can therefore be any sign, symptom, or disease, or any worsening of an existing sign, symptom, or disease, whether or not considered related to the study product or trial procedures, including injuries.

Any medical condition that is present at the time of Screening or Baseline should be considered as medical history and reported on the medical history CRF and should not be reported as an adverse event except for adverse events observed at the Baseline Visit due to study procedures performed at the Screening Visit which should be reported (except for worsening of psoriasis). Anticipated day-to-day fluctuations of pre-existing conditions should not be reported as adverse

events. Unexpected worsening of pre-existing conditions should be reported as adverse events. The disease or condition being studied or expected progression, signs, or symptoms of the disease or condition being studied should not be reported as an adverse event unless more severe than expected.

All serious adverse events, all study-product-related adverse events and all adverse events leading to study product discontinuation must be followed until the clinical outcome is determined or until all attempts to determine resolution of the event are exhausted ("not recovered" is not an acceptable outcome for acute conditions). For other adverse events, the status at the last visit can be entered into the CRF.

8.1 Adverse Event Reporting Period

Adverse event data must be collected from the time treatment is initiated until study product treatment is discontinued except for spontaneously reported serious adverse events which should be reported up to 30 days after discontinuing study product use and entered on the CRF. Adverse events occurring from the time of the Screening Visit until the Baseline Visit associated with study procedures should also be reported for all subjects including screen failures. Abnormal screening ACTH stimulation test should not be reported as an adverse event. Abnormal End of Treatment ACTH stimulation tests will be recorded as adverse events of HPA axis suppression related to study product and will be repeated until HPA axis is stabilized (or explained).

8.2 Recording Adverse Events

The investigator will record all adverse events, regardless of relationship to study product on the adverse event CRF. Standard medical terminology should be used when describing adverse events. Whenever possible a diagnosis should be made and recorded on the CRF rather than listing signs and symptoms. Intermittent adverse events can be recorded once. The anatomical location of the adverse event must be specified, when applicable, as well as whether the location is a treatment area. The following information should be recorded on the CRF:

1. Description
2. Start date
3. Stop date or date of death, ongoing, or unknown
4. Severity of the event (see 8.3.1: Severity for details)
5. Study product use continued or not
6. Outcome of the event (recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, unknown, fatal)
7. Relationship to study product (see 8.3.2: Relationship to Study Product (Causality) for details)
8. Indication of whether the event is serious (see 8.3.3: Seriousness for details)
9. Actions taken including treatment with concomitant medication

8.3 Assessment of Adverse Events

8.3.1 Severity

It is the investigator's responsibility to assess the severity of each adverse event. Descriptions of severity are as follows:

1. Mild: Awareness of sign or symptom, but easily tolerated. Not likely to interfere with normal activity or require medical attention.

2. Moderate: Discomfort enough to cause interference with usual activity. May require medical intervention.

3. Severe: Incapacitating such that normal activity is prevented. Likely requires medical intervention and/or close follow-up.

8.3.2 Relationship to Study Product (Causality)

It is the investigator's responsibility to assess the relationship between the study product and the adverse event. The degree of "relatedness" of the adverse event to the study product should be described using the following categories:

1. Not Related: The event is clearly due to extraneous causes (e.g., diseases, environment, etc.). Specify if known. Or, the event is most probably produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant therapy and does not follow a known response pattern to the study product.

2. Possibly Related: The event is temporally related to study product use but can be explained by another etiology. Information on the effect of study product withdrawal may be lacking.

3. Probably Related: The event is temporally related to study product use and is consistent with known effects of the study product and/or improves upon withdrawal of the study product.

4. Definitely Related: The event follows a reasonable temporal sequence from the time of study product administration and/or follows a known response pattern to the study product, and could not have been produced by other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy, and either occurs immediately following study product administration, or improves on stopping the product, or there is a positive reaction at the application site.

8.3.3 Seriousness

It is the investigator's responsibility to determine the "seriousness" of an adverse event. A serious adverse event (SAE) is any adverse event occurring at any dose that results in any of the following outcomes:

1. Death
2. Life-threatening (subject at immediate risk of death)
3. Inpatient hospitalization or prolongation of hospitalization
4. Results in persistent or significant disability/incapacity
5. Results in congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.4 Reporting Serious Adverse Events

SAE information must be faxed or emailed within 24 hours of becoming aware of the event. The minimum *initial* information required to be reported on the Serious Adverse Event Form is: the protocol number, site number, subject number, subject initials, the event, the causality, the date of the event and the name and contact information (email, phone number) of the person reporting the event. This initial report should be promptly followed up with a *completed* Serious Adverse Event Form.

Serious Adverse Events: Shahida Hasan, M.D., M.S.
Fax: 609 228-5408
Email: DFD01-CD-013@promiuspharma.com

The initial information must include a causality assessment that is provided by the primary investigator or other medically qualified individual. The causality assessment can be amended as more information is available. Significant new information about ongoing SAEs should be reported promptly to the sponsor.

Serious adverse events will be evaluated by the Medical Monitor within 24 hours of receipt and plans for management and further reporting (i.e. FDA) determined.

8.5 Discontinuation Due to an Adverse Event

The sponsor must be notified within 5 days if any subject is withdrawn or discontinues study product use due to an adverse event if AE is related to the study product (see title page for contact information).

8.6 Exposure *in utero* (Pregnancy)

If a female subject becomes pregnant during the study, study product must be discontinued immediately and she must be followed through the pregnancy and delivery. The investigator should report the event to the sponsor immediately (see contact information on title page) and complete the Pregnancy Surveillance Form. The expected date of delivery or expected date of the end of the pregnancy should be included in this information. The investigator is instructed to

contact the subject every 3 months until the end of her pregnancy and report the outcome to the sponsor. Details of the pregnancy, delivery and health of the infant should be recorded on the Pregnancy Surveillance Form.

The following outcomes of pregnancy fall under the criteria for serious adverse events and should be reported as such: delivery complications prolonging hospitalization, spontaneous abortion, stillbirth, death of newborn baby, congenital anomaly, and anomaly in a miscarried fetus.

9 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act. This regulation requires a signed authorization informing the subject's legal guardian of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject's legal guardian to revoke the authorization for use/disclosure of subject's PHI
- Expiration of authorization

In the event that a subject's legal guardian revokes authorization to collect and use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of authorization. For subjects that have revoked authorizations to collect and use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Investigators must keep accurate separate records (other than CRFs) of all subject visits which include all pertinent study related information including original signed/dated informed consent forms. Source documents for this study include all written records of study data. All study data must have a paper source document including investigator assessments.

9.3 Screening/Enrollment Log

A subject Screening/Enrollment Log, noting reasons for screen failure where applicable, must be maintained for all subjects who are consented. The log should also include subject initials, screening date, subject number, randomization number, assigned product and date and time of randomization, where applicable.

9.4 Case Report Forms

The study case report form (CRF) for the study is a paper document which will be completed by the sites. All data requested on the CRF must be recorded on source documentation. The CRF

cannot be the source document for any data. Detailed instructions and training for completing the CRF will be provided to the sites.

Study subjects are not to be identified by name on CRFs, but rather by coded identifiers (subject number and initials). The investigator or sub-investigator must review all CRF pages for each subject and approve the group of CRFs pages for each subject.

9.5 Data Capture

Study data will be entered into and maintained in a 21 CFR Part 11 compliant database.

9.6 Archiving of Study Documentation

The investigator must retain study records for 2 years following the date a marketing application is approved for the investigational product; or, if the application is not filed or is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

The sponsor will inform the investigator, in writing, as to when these documents no longer need to be maintained.

All study documents, original source documents, correspondence, IRB documents, etc. are subject to sponsor and FDA inspection at any time.

10 MONITORING AND DATA QUALITY ASSURANCE

Only persons who are appropriately trained and who have the scientific and clinical knowledge to adequately monitor the study will be selected for monitoring this study. The monitor must have at least one year previous experience in monitoring clinical studies. The monitor should be familiar with the etiology and signs and symptoms of psoriasis and the treatment options that are currently available.

Before study initiation, the investigator and site personnel will receive protocol training from the sponsor's representatives to ensure collection of accurate, consistent, complete and reliable data. This training will take place either at an Investigator Meeting or individually on-site.

During the course of the study, a monitor will make multiple site visits to check the progress of the study, review consent forms, review protocol compliance, assess drug accountability, and ensure that the study is being conducted according to the protocol and Good Clinical Practice. Any review of the subjects' original medical records will be performed in a manner to ensure that subject confidentiality is maintained. The investigator will ensure that the monitor or other compliance auditor is given access to all study-related documents and has adequate time and space to conduct the monitoring visit including availability of the investigator and site personnel to discuss findings.

Data capture methods will be designed to ensure accurate transfer of data to electronic media.

The sponsor's Quality Assurance representative will conduct QA audits randomly or if needed at 5-10% of the investigator sites.

11 STATISTICAL CONSIDERATIONS

All statistical processing will be performed using SAS® unless otherwise stated. Descriptive statistics will be used to summarize the data. No inferential testing will be performed. All summaries will be performed on the safety population.

No interim analyses are planned.

No imputations will be made for missing data.

A Statistical Analysis Plan, describing all statistical analyses, will be provided as a separate document prior to database lock.

11.1 Sample Size

Approximately 50 subjects will be randomized to the two treatment groups in a 1:1 ratio for 25 subjects per group. No statistical justification has been made for the sample size.

11.2 Analysis Data Set

All summaries will be performed on the safety population. All subjects who receive at least one confirmed dose of study product and provide any post-baseline safety information will be included in the safety population. No imputation will be made for missing safety data.

11.3 Demographic and Baseline Data

Subject demographic and Baseline characteristics will be summarized by treatment group for the safety population. For continuous variables (e.g., age, BSA), descriptive statistics including sample size N, mean, median, standard deviation, minimum, and maximum will be presented. For categorical variables (e.g., IGA), descriptive statistics including N, frequency count and percentages will be presented.

11.4 Efficacy Summary

Descriptive statistics will be used to summarize IGA by treatment group and visit and will include sample size, frequency counts, and percentages.

11.5 Safety Summaries

Descriptive statistics will be presented to summarize the safety data. Continuous variables will be summarized with sample size N, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with sample size N, frequency counts and percentages.

11.5.1 Extent of Exposure

The extent of exposure to study product in both treatment groups will be summarized as the total number of applications and the total amount of study product used based on bottle weights. The amount of the last dose will be provided based on bottle weight before and after treatment.

11.5.2 Local Safety Evaluation

Atrophy, telangiectasia, burning/stinging, pain, or itching will be summarized by treatment group and visit.

11.5.3 ACTH Stimulation Test

The proportion of subjects with abnormal serum cortisol response for ACTH stimulation test at the end of treatment (cortisol level ≤18 ug/dL at 30 minutes post stimulation) will be summarized by treatment group. Additionally, the serum and saliva cortisol levels found pre-stimulation and post-stimulation will be summarized for the screening ACTH test and the end of treatment ACTH test. The sample size N, mean, median, standard deviation, minimum, and maximum saliva cortisol levels will be provided for the subsets of subjects with abnormal and normal serum cortisol response.

11.5.4 Pharmacokinetics

The plasma concentrations of betamethasone, betamethasone-17-propionate, and betamethasone -17,21-dipropionate will be summarized (and will include 95% confidence intervals for the mean) for the PK Screening sample and for 0 (pre-treatment), 1, 3, and 6 hours (±5 minutes) after the last application of study product at the end of treatment. The average of the post-treatment concentrations will also be summarized. Plasma concentrations that are taken more than 1 hour off-schedule will be included in data listings only and will not be included in the summarization of the concentration data.

11.5.5 Adverse Events

All AEs occurring during the study will be recorded and classified on the basis of MedDRA terminology. Treatment-emergent adverse events are those AEs with an onset on or after the date of the first study product administration. For the safety population, all reported treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting events, system organ class, preferred term, severity, relationship to study product, and seriousness. When summarizing AEs by causality and severity, each subject will be counted only once within a system organ class or a preferred term by using the event with the greatest relationship and highest severity within each classification.

Serious adverse events (SAEs) will be summarized by treatment group, severity, and relationship to study product, and SAEs will be listed by subject. In addition, a list of subjects who prematurely discontinued from the study due to an AE will be provided.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim term given by the investigator, preferred term, system organ class, onset date,

resolution date, maximum severity, seriousness, action taken regarding study product, corrective treatment, outcome, and drug relatedness. The event onset will also be shown relative (in number of days) to date of first administration.

AEs related to study procedures done before study product administration will be provided in a data listing.

11.5.6 Vital signs

Changes from Baseline in vital signs (blood pressure, pulse) will be summarized by treatment group at each evaluation.

11.5.7 Safety Laboratory Values

Urine pregnancy tests will be performed at all visits for female subjects and will be presented in subject data listings.

11.5.8 Subset Analyses

No subset analyses are planned.

12 REFERENCES

Finlay AY. Current severe psoriasis and the rule of tens. Br J Dermatol. 2005;152:861-867.

Gallagher P, Leitch MM, Massey AE, et al. Assessing cortisol and dehydroepiandrosterone (DHEA) in saliva: effects of collection method. J Psychopharmacol. 2006;20(5):643-9.

Mendonca CO, Burden AD. Current concepts in psoriasis and its treatment, Pharmacol & Therapeutics. 2003;99(2):133-147.

Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. *J Am Acad Dermatol*. 2008;58(5):826-850.

Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et.al Guidelines of care for the management of psoriasis and psoriatic arthritis. *J Am Acad Dermatol.* 2009;60(4):643-659.

National Psoriasis Foundation. Psoriasis Prevalence. http://www.psoriasis.org/netcommunity/learn_statistics. Accessed October 27, 2010.

Study BDS1307. A Randomized, Parallel, Open Label, Multicenter Study to Assess the Potential for Adrenal Suppression and Systemic Drug Absorption Following Multiple Dosing with Betamethasone Dipropionate Spray 0.05% versus Diprolene® (augmented betamethasone dipropionate) Lotion 0.05% in Subjects with Moderate to Severe Plaque Psoriasis. February, 2015.

APPENDIX 1
Declaration of Helsinki (2013)

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

A. PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

B. GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the international Code of Medical Ethics declares that,”A physician shall act in the patient’s best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

C. RISK, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

D. VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical Research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

E. SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions

for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

F. RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

G. PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

H. INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to

the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

I. USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
    a. Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    b. Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

J. POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

K. RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.
37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This

intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

October 2013

APPENDIX 2
Subject Instructions - Spray

1. You have been given a bottle of study medication. **Shake well before using**. Spray study medication directly onto each of your psoriasis lesions as instructed by the study nurse. Refer to the diagram provided. Apply study medication to all areas shown on the body diagram even if clear. Also apply study medication to new areas that may appear between visits. Apply study medication in the morning and at bedtime, approximately 12 hours apart. You will need to use at least 15-20 sprays of study medication each time. You can use more if needed. Massage lightly after application until medication disappears. If bathing at the treatment time, apply medication after bathing.

2. The study medication is for external use only. The study medication should not be used on the scalp, face, underarms, or groin area. Also avoid contact with eyes and lips. The application areas must not be bandaged, covered, or wrapped.

3. Always wash hands before applying the study medication and thoroughly after applying.

4. Store medication at room temperature.

5. If you have any questions, please ask the study coordinator or nurse.

6. The study medication may cause some irritation or discomfort. Tell your doctor about any reactions. If the reaction becomes severe, stop using the study medication and call the doctor.

7. Write down the date and time (am or pm) when you apply the study medication in your study diary.

8. Do not let anyone else use the study medication. Keep the medication out of the reach of children and pets. Use of the study product should be done under the supervision of the legal guardian.

9. Return all containers in the box at every study visit.

10. Bring your study diary to every visit.

11. If you cannot make a scheduled visit, please contact the study office as soon as possible to re-schedule another date.

12. Do not use study medication on the morning of your last study visit.

13. If you have to discontinue participation in the study for any reason, notify the study office immediately. A visit will be scheduled for a final examination of psoriasis and to collect the containers and your diary. This visit is important for your safety.