

## Clinical Study Protocol

**IDP-122**

**Protocol V01-122A-301**

### **A Phase 3, Multicenter, Double-Blind, Randomized, Vehicle Controlled Clinical Study to Assess the Safety and Efficacy of IDP-122 in the Treatment of Plaque Psoriasis**

Development phase of study:	3
Study design:	Multicenter, Double-Blind, Randomized, Vehicle Controlled Clinical Study
Date: Original	14 July 2015
<b>Amendment 1</b>	<b>14 October 2015</b>
Sponsor:	Dow Pharmaceutical Sciences, a Division of Valeant Pharmaceuticals North America, LLC 1330 Redwood Way Petaluma, CA 94954 [REDACTED]

**CONFIDENTIAL**

**Nothing herein is to be disclosed without prior approval of the sponsor.**



## Protocol Review and Approvals

**A Phase 3, Multicenter, Double-Blind, Randomized, Vehicle Controlled Clinical Study  
to Assess the Safety and Efficacy of IDP-122 in the Treatment of Plaque Psoriasis**

**Reviewed and approved:**

[Redacted]

Valeant Pharmaceuticals North America LLC

[Redacted]

Signature

Date

[Redacted]

Valeant Pharmaceuticals North America LLC

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Signature

Date

[Redacted]

Valeant Pharmaceuticals North America LLC

[Redacted]

Signature

Date

## Personnel Responsible for Conducting the Study

### A Phase 3, Multicenter, Double-Blind, Randomized, Vehicle Controlled Clinical Study to Assess the Safety and Efficacy of IDP-122 in the Treatment of Plaque Psoriasis

#### Contract Research Organization

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## Principal Investigator Protocol Agreement Page

I agree:

- To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol, written informed consent, consent form updates, subject-recruitment procedures (e.g., advertisements), and any other written information to be provided to the subjects, before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study.
- To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies).
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current Investigator Brochure or equivalent document and approved product label (if applicable).
- To provide sufficient time, and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study related duties and functions.

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Principal Investigator (print name)

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Principal Investigator (signature)

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Date

## 2 Synopsis

<b>Name of Sponsor/Company:</b> Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America, LLC
<b>Name of Investigational Product:</b> IDP-122 Lotion
<b>Name of Active Ingredients:</b> Halobetasol propionate (HP) 0.01% w/w
<b>Title of Study:</b> A Phase 3, Multicenter, Double-Blind, Randomized, Vehicle Controlled Clinical Study to Assess the Safety and Efficacy of IDP-122 in the Treatment of Plaque Psoriasis
<b>Number of clinical centers:</b> Multicenter, approximately 12-16 investigational centers in North America
<p><b>Objective:</b></p> <p>The objective of the study is to evaluate the safety and efficacy of topical IDP-122 Lotion when applied once daily to adult subjects with moderate to severe plaque psoriasis (defined as an Investigator's Global Assessment [IGA] score of 3 or 4). The intent of the study is specifically to evaluate the safety and efficacy of a once daily application of IDP-122 Lotion in comparison with vehicle.</p>
<p><b>Methodology:</b></p> <p>This is a multicenter, double-blind, randomized, parallel-group study designed to assess the safety, tolerability, and efficacy of IDP-122 Lotion in comparison with vehicle. To be eligible for the study, subjects must be at least 18 years of age and have a clinical diagnosis of moderate to severe psoriasis (defined as an IGA score of 3 or 4).</p> <p>Approximately 210 subjects who meet the study entry criteria will be randomized in a 2:1 ratio to receive IDP-122 (HP 0.01%) Lotion and IDP-122 Vehicle Lotion, respectively. Two containers of the assigned study drug will be dispensed to the subject at the Baseline visit. The study drug will be applied topically to the affected areas (as determined by the investigator at baseline) once daily for 8 weeks. The initial application will be made by the subject per instruction from the study staff. The subjects will be instructed to avoid exposure to direct sunlight, artificial ultraviolet light sources and to use protective clothing to prevent sunburn. Subjects will apply their once daily treatments at home as explained by the study coordinator or designee at each investigational center.</p> <p>The study coordinator, or designee at each investigational center will dispense 2 new containers of study drug to each subject at Baseline and Weeks 2, 4, and 6. During post-baseline study visits (Weeks 2, 4, 6, and 8) the subjects will be asked to return their containers of study drug which will be evaluated for drug usage compliance. Upon completion of the 8-week treatment period, all subjects will be asked to return to the investigational center 4 weeks later for a post-treatment cessation follow-up visit (Week 12). During the study, subjects will be allowed to use investigator approved non-medicated cleansers, moisturizers and sunscreens; no other skin care products will be permitted on the treatment areas. The investigator will assess the areas affected by psoriasis at each study visit.</p> <p>All areas affected by psoriasis (with an affected body surface area [BSA] of 3%-12%, inclusive) are to be treated with study drug. The affected areas (3%-12% BSA) will not include face, scalp, palms, soles, groin, axillae, and intertriginous areas. Information on reported and observed adverse events (AEs) will be obtained at each visit. An abbreviated physical examination will be performed at Baseline, Week 8 (end of treatment), and Week 12 (4-week post-treatment cessation follow-up visit) for all subjects.</p> <p>Blood samples for complete blood count with differential (CBC/Diff) and serum chemistry will be collected from subjects at Screening, Week 4, and Week 8. For all female subjects of childbearing potential, urine and serum pregnancy testing will be performed at Screening. Urine pregnancy testing will be performed at Baseline (prior to randomization) and Week 12 (4-week post-treatment follow-up visit), and serum pregnancy testing will also be conducted at Week 4 and Week 8.</p> <p>Subjects who terminate study participation early will be asked to complete all Week 8 assessments, as appropriate, prior to commencement of any alternative therapy for psoriasis (if possible). Subjects who discontinue from the study during the treatment period will not be replaced and these subjects may be asked to return for the 4-week follow-up visit after the last treatment visit.</p>

If signs or symptoms develop in the selected treatment areas during the treatment period that restrict daily activities or make continued application of the study drug difficult due to discomfort, the investigator may instruct the subject to temporarily interrupt use of the study drug and to resume application of the study drug once the signs/symptoms have subsided. The investigator should try to minimize study drug interruptions; and if needed, make best efforts to limit a “drug holiday” to 4 days. If the study drug interruption does exceed 4 consecutive days, the investigator should consult with the medical monitor to determine a course of action. If the study drug is interrupted, discontinued, or a concomitant medication is used to treat a sign/symptom, an adverse event shall be recorded.

Subjects who discontinue from the study, due to clinically significant laboratory abnormalities or AEs will return for the 4-week follow-up visit after the last treatment visit and will be instructed to follow-up with their primary care physician, if indicated. If any subject who has an AE, during the treatment period, the subject will be followed by the investigator until resolution (return to normal or to the baseline state) or stabilization, as determined by the investigator.

In addition, application of study drug may be delayed or halted at any time if ongoing safety data evaluations (including reports of local skin reactions, such as skin atrophy, or severe AEs) raise concern for subject safety. If the subject participation is suspended, all of the subject’s safety data will be reviewed by the medical monitor in conjunction with the investigator to determine course of action.

**Number of subjects planned:**

Approximately 210 adult subjects (approximately 15 subjects per investigational center) with moderate or severe psoriasis (defined as an IGA score of 3 or 4) will be enrolled and randomized in the study. With a 2:1 randomization ratio, it is anticipated that:

- Approximately 140 subjects will be randomized to receive IDP-122 (HP 0.01%) Lotion
- Approximately 70 subjects will be randomized to receive IDP-122 Vehicle Lotion

**Diagnosis and main criteria for inclusion:**

1. Male or female, of any race, at least 18 years of age.
2. Freely provides both verbal and written informed consent.
3. Has an area of plaque psoriasis appropriate for topical treatment that covers a BSA of at least 3%, but no more than 12%. The face, scalp, palms, soles, axillae, and intertriginous areas are to be excluded in this calculation.
4. Has a clinical diagnosis of psoriasis at the Baseline visit with an IGA score of 3 or 4. (The face, scalp, palms, soles, axillae, and intertriginous areas are to be excluded from this assessment, if psoriasis is present).
5. Has a target lesion that meets the following criteria:
  - Measures between 16-100 cm<sup>2</sup> inclusive
  - Has a score of at least 3 for at least 2 of the 3 different psoriasis signs (erythema, plaque elevation, and scaling); with a sum of the three scores at least eight (8), and cannot have a score of 0 or 1 for any one of the signs
  - Target lesions cannot be on excluded areas or areas covering bony prominences (i.e., elbows and knees)
6. Is in good general health based on the subject’s medical history and a physical examination, Screening hematology and serum chemistry laboratory values within normal range or not clinically significant as determined by the investigator.
7. If female and of childbearing potential, must have a negative urine and serum pregnancy test at the Screening visit and negative urine pregnancy at Baseline visit prior to randomization.
8. If female, is either not of childbearing potential, defined as postmenopausal for at least 12 months or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or is of childbearing potential and practicing 1 of the following methods of birth control throughout the study:
  - Condom with spermicide, diaphragm with spermicide, intrauterine device, or abstinence
  - Stable use of a hormonal contraceptive (oral, implant, insertable, injection or transdermal patch) for at least 3 months prior to the Baseline visit.
9. Subject is willing to comply with study instructions and return to the clinic for required visits.

<p><b>Key exclusion criteria:</b></p> <ol style="list-style-type: none"> <li>1. Has spontaneously improving or rapidly deteriorating plaque psoriasis or pustular psoriasis, as determined by the investigator.</li> <li>2. Presents with psoriasis that was treated with prescription medication and failed to respond to treatment, even partially or temporarily, as determined by the investigator.</li> <li>3. Presents with any concurrent skin condition that could interfere with the evaluation of the treatment areas, as determined by the investigator.</li> <li>4. Is pregnant, nursing an infant, or planning a pregnancy during the study period.</li> <li>5. Has received treatment with any investigational drug or device within 60 days or 5 drug half-lives (whichever is longer) prior to the Baseline visit, or is concurrently participating in another clinical study with an investigational drug or device.</li> <li>6. Received treatment with any topical antipsoriatic drug product within 14 days prior to the Baseline visit.</li> <li>7. Has used any phototherapy (including laser), photochemotherapy, or non-biologic systemic psoriasis therapy (such as newer oral psoriasis medications (eg Otezla), systemic corticosteroids, methotrexate, retinoids or cyclosporine) within 4 weeks prior to the Baseline visit.</li> <li>8. Has used immunomodulatory therapy (biologics) known to affect psoriasis within 3 months of the Baseline visit.</li> <li>9. Has had prolonged exposure to natural or artificial sources of ultraviolet radiation within 4 weeks prior to the Screening visit or is intending to have exposure during the study thought likely by the investigator to modify the subject's psoriasis.</li> <li>10. Is currently using lithium or Plaquenil.</li> <li>11. Has a history of hypersensitivity or allergic reaction to any of the study drug constituents.</li> <li>12. Is unable to be compliant with study procedures, study drug administration requirements, study visit schedules, and prohibitions regarding the use of concomitant medications/therapies.</li> <li>13. Is unable to communicate or cooperate with the investigator.</li> <li>14. Has any underlying disease that the investigator deems uncontrolled that poses a concern for the subject's safety while participating on the study.</li> <li>15. Has a history of drug or alcohol abuse.</li> <li>16. Is considered by the investigator, for any other reason, to be an unsuitable candidate for the study.</li> </ol>
<p><b>Investigational product, dosage and mode of administration:</b> IDP-122 Lotion, applied topically, once daily for 8 weeks.</p> <p><b>Application Instructions:</b> The investigational center staff member will instruct the subject to apply the study drug to the affected treatment areas identified at the Baseline visit by the investigator. The staff member will instruct the subject on the proper application procedure during the Baseline visit. Subjects will be instructed to squeeze a small amount of study drug (about the size of a pea) onto a fingertip and then spread a thin layer of the study drug over the affected treatment area. If necessary, additional pea-sized amounts of study drug may be applied in increments to cover all affected treatment areas as designated by the investigator. In addition to the verbal instructions given during the visit, the subjects will be provided with written instructions. Subjects will be instructed to apply a thin layer of study drug to the entire selected treatment area(s) as indicated on the body diagram at home once daily up to the Week 8 visit. Subjects will be advised to avoid or minimize exposure to direct sunlight and artificial ultraviolet light sources while in the study and to wash their hands before and after application of the study drug. The amount of study drug used by the subjects will be monitored by weighing each newly dispensed study drug container and re weighing each returned study drug container at all applicable study visits. The maximum allowable weekly usage is 50 grams for this study.</p>
<p><b>Duration of treatment:</b> 8 weeks for all subjects</p>

<p><b>Reference therapy, dosage and mode of administration:</b>                  IDP-122 Vehicle Lotion, applied topically, once daily for 8 weeks.                  The reference therapy (IDP-122 Vehicle Lotion) will be applied in the same manner as described for the investigational product (IDP-122 Lotion).</p>		
<p><b>Criteria for evaluation:</b>                  A summary of the study measurements follows. Note that for all efficacy measurements, the investigators/evaluators will be provided with training to ensure consistent evaluations across investigational centers. To the greatest extent possible, the assessments for a particular subject should be performed by the same sponsor-approved evaluator at all study visits.</p>		
<p><b>Safety Measurements:</b>  <u>Local Skin Reactions:</u> Tolerability will be evaluated through assessments of selected local signs and symptoms (itching, dryness, burning/stinging). In addition, the treatment areas will be examined at each visit by the evaluator for the presence or absence of significant known drug-related AEs; skin atrophy, striae, telangiectasia, and folliculitis. Any local skin reaction requiring use of a concomitant therapy or is a cause for study drug interruption or discontinuation should be reported as an adverse event. The scales to be used for assessing local skin reactions follow:</p>		
<b>Score</b>	<b>Grade</b>	<b>Description</b>
<i>Itching: as reported by the subject within the last 24 hours</i>		
0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching that is somewhat bothersome
3	Severe	Intense itching that may interrupt daily activities and/or sleep
<i>Dryness: as assessed by the investigator</i>		
0	None	No dryness
1	Mild	Slight, but definite roughness
2	Moderate	Definite roughness
3	Severe	Marked roughness
<i>Burning/Stinging: as reported by the subject within the last 24 hours</i>		
0	None	No burning/stinging
1	Mild	Slight burning/stinging sensation; not really bothersome
2	Moderate	Definite warm, burning/stinging that is somewhat bothersome
3	Severe	Hot burning/stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep



<i>All of the below will be assessed by the investigator as present or absent.</i>	
Skin Atrophy:	
No	Skin atrophy not present
Yes	Skin atrophy present
Striae:	
No	Striae not present
Yes	Striae present
Telangiectasias:	
No	Telangiectasias not present
Yes	Telangiectasias present
Folliculitis:	
No	Folliculitis not present
Yes	Folliculitis present

Adverse Events: During the study, subjects will be assessed for the occurrence of new and ongoing AEs. Descriptions of AEs will include the dates of onset and resolution (if resolved), maximum severity, seriousness, action taken regarding the study drug, corrective treatment, outcome, and the investigator’s assessment of causality. AEs present at any visit will be followed to resolution (return to normal or to the baseline state) or until clinically stable as determined by the investigator.

Safety Laboratory Tests: Routine safety laboratory tests (CBC/Diff and serum chemistry) will be performed at Screening, Week 4, and Week 8. Any out-of-range laboratory result that is considered clinically significant by the investigator will be recorded as an AE and should be confirmed by repeat testing at the discretion of the investigator. Clinically significant laboratory abnormalities at any visit will be followed to resolution (return to normal or to the baseline state) or until clinically stable as determined by the investigator.

Pregnancy Tests: All female subjects of childbearing potential will undergo serum pregnancy testing at Screening, Week 4, and Week 8. In addition, urine pregnancy testing will be performed at Screening, Baseline (prior to randomization), and Week 12 (4-week post-treatment follow-up visit).

Abbreviated Physical Examinations: An abbreviated physical examination will be performed at Baseline, Week 8, and Week 12 (4-week post-treatment follow-up visit).

**Efficacy Measurements:**

Investigator's Global Assessment: The IGA is based on a 5-point scale ranging from 0 (clear) to 4 (severe), and will be assessed by the evaluator at each visit for the overall affected areas with plaque psoriasis. The face, scalp, palms, soles, axillae, and intertriginous areas are to be excluded in this assessment. The following scores will be used to describe the severity of overall psoriasis of the treatable areas:

<b>Grade</b>	<b>Score</b>	<b>Description</b>
Clear	0	No evidence of scaling No evidence of erythema No evidence of plaque elevation above normal skin level
Almost Clear	1	Some plaques with fine scales Faint pink/light red erythema on most plaques Slight or barely perceptible elevation of plaques above normal skin level
Mild	2	Most to all plaques have some fine scales but are not fully covered, some plaques are completely covered with fine scale Most to all plaques are pink/light red to bright red in color Some plaques have definite elevation above normal skin level, typically with edges that are indistinct and sloped on some of the plaques
Moderate	3	Some plaques are at least partially covered with a coarse scale, most to all plaques are nearly covered with fine or coarse scale; Most to all plaques are bright red, some plaque may be dark red in color Definite elevation of most to all plaques; rounded or sloped edges on most of the plaques
Severe	4	Most to all plaques are covered with coarse, thick scales Most or all plaques are bright, dark or dusky red Almost all plaques are raised and well-demarcated; sharp edges on virtually all plaques

**Psoriasis Signs:** The signs of psoriasis (erythema, plaque elevation, and scaling) will be assessed by the evaluator using the following scales for the selected target lesion:

Score	Grade	Description
<i>Erythema:</i>		
0	None	No erythema
1	Minimum	Pink discoloration, minimal erythema
2	Mild	Most plaques are light red to red in color
3	Moderate	Most or all plaques are bright red or dark red in color
4	Severe	Most plaques dusky red with purple hue
<i>Plaque Elevation:</i>		
0	None	No evidence elevation above the normal skin level
1	Minimum	Slight, just discernible elevation above normal skin level
2	Mild	Some plaques show definite elevation with indistinct edges
3	Moderate	Most plaques have definite elevation with distinct edges that are rounded or sloped
4	Severe	Almost all plaques are raised above normal skin level with sharp edges
<i>Scaling:</i>		
0	None	No scales on very few plaques
1	Minimum	Occasional fine scales hardly noticeable
2	Mild	Most plaques have fine scales
3	Moderate	Some plaques have coarse scales while most plaques have fine scales
4	Severe	Most plaques are covered by thick coarse scales

**Other Evaluations:**

**Questionnaire:** The Dermatology Life Quality Index (DLQI) questionnaire will be administered to subjects at Day 0 (Baseline), Week 4, Week 8/End of Treatment and Week 12 (4-week post-treatment follow-up visit).

**Photography:** Standardized photographs will be taken starting at the baseline visit and at all subsequent study visits of one target lesion and one other psoriasis lesion.

**Statistical methods:**

All subjects who are randomized and dispensed study drug will be included in the intent-to-treat (ITT) analysis set. All subjects in the ITT analysis set who complete the Week 8 visit without any major protocol violations will be included in the per protocol (PP) analysis set. All subjects who are randomized, receive at least 1 confirmed dose of study drug, and have at least 1 post-baseline assessment will be included in the safety analysis set.

The ITT analysis set will be considered primary for the evaluation of efficacy. The primary method of handling missing efficacy data will be the method of Markov Chain Monte Carlo (MCMC) multiple imputation; no imputations will be made for missing safety data.

*Efficacy:*Efficacy Endpoints

The efficacy endpoints are intended to compare once daily application of IDP-122 Lotion and vehicle. Specifically, the efficacy endpoints include:

- The percent of subjects with treatment success, defined as at least a 2 grade improvement from Baseline in the IGA score and an IGA score equating to “clear” or “almost clear” at Weeks 2, 4, 6, 8 and Week 12 (4-week follow-up), as summarized using descriptive statistics.
- The percent of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Weeks 2, 4, 6, 8 and Week 12 (4 week FU), as summarized using descriptive statistics for the target lesion treated with study drug.

Inferential Statistics

## Primary Efficacy

The primary efficacy endpoint will be the percent of subjects with treatment success, defined as at least a 2-grade improvement from Baseline in IGA score and an IGA score equating to “Clear” or “Almost Clear”. The primary efficacy endpoint will be used to compare once daily application of IDP-122 Lotion with its vehicle. The percent of subjects with treatment success at Week 8 will be analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by analysis center.

## Secondary Efficacy

Similar to the primary endpoint analyses, pairwise comparisons will be performed using CMH tests stratified by analysis center. The secondary efficacy endpoints will be:

- Percentage of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at Week 12 for IDP-122 Lotion versus IDP-122 Vehicle Lotion
- Percentage of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at Week 6 for IDP-122 Lotion versus IDP-122 Vehicle Lotion
- Percentage of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at Week 4 for IDP-122 Lotion versus IDP-122 Vehicle Lotion
- Percentage of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at Week 2 for IDP-122 Lotion versus IDP-122 Vehicle Lotion

Evaluation of the secondary efficacy variables will use a gated sequential procedure starting with the comparisons of the first bulleted item and proceeding onto the next item. The process will terminate if a nonstatistically significant value is observed.

### Tertiary Efficacy

The follow tertiary efficacy endpoints will be analyzed to further characterize the treatment effect of IDP-122 Lotion over the IDP-122 Vehicle Lotion. The analyses will use CMH testing stratified by analysis center without adjusting for multiplicity.

- Percentage of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Week 8 for the target lesion
- Percentage of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Week 12 for the target lesion
- Percentage of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Week 6 for the target lesion
- Percentage of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Week 4 for the target lesion
- Percentage of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Week 2 for the target lesion

### *Safety:*

Subjects will be assessed for the occurrence of new and ongoing AEs. Descriptions of AEs will include the dates of onset and resolution (if resolved), maximum severity, seriousness, action taken regarding the study drug, corrective treatment, outcome, and investigator's assessment of causality. All AEs will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent AEs (TEAEs), defined as any AE with an onset on or after the date of first study drug application, will be summarized by treatment group, the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to study drug. When summarizing TEAEs by severity or relationship to study drug, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported serious adverse events (SAEs) will be summarized by treatment group, the number of subjects reporting SAEs, system organ class, preferred term, severity, and relationship to study drug.

All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the investigator, as well as the preferred term, system organ class, start date, stop date (if stopped), seriousness, severity, action taken regarding the study drug, corrective treatment, outcome and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided as well as a listing of subjects who reported an SAE.

The frequency of local skin reactions including itching, dryness, burning/stinging, skin atrophy, striae, telangiectasia and folliculitis will be summarized by treatment group and visit. Additionally, the percent of subjects who experience a local skin reaction (itching, dryness, burning/stinging) graded at a level of 3, at any point in the study following the first application of study drug, will be tabulated by treatment group. Changes from baseline in safety laboratory values and vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits.

Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at Baseline and Weeks 4 and 8. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment time point will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

**Sample size calculations:**

One hundred forty (140) IDP-122 treated subjects and seventy (70) vehicle treated subjects will have greater than 95% power to detect a statistically significant outcome for a two-sided test with an alpha level of 0.05. This is based on treatment success rates of 33.3% and 9.7% which were observed in V01-118A-201. Success was defined as at least a 2-grade improvement from Baseline in the IGA score and an IGA score equating to “Clear” or “Almost Clear”.

This study will be performed in compliance with GCP including the archiving of essential study documents. This protocol follows guidelines outlined by the International Conference on Harmonization (ICH). All data furnished to the investigator and his/her staff, and all data obtained through this study, will be regarded as confidential and proprietary in nature and will not be disclosed to any third party, except for the United States Food and Drug Administration or other regulatory body, without written consent from the sponsor.

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## 4 List of Abbreviations and Definitions of Terms

Abbreviation or Specialist Term	Definition or Explanation
AE	Adverse event
BSA	Body surface area
CBC/Diff	Complete blood count with differential
CMH	Cochran-Mantel-Haenszel
eCRF	Electronic Case Report Form
DLQI	Dermatology Life Quality Index questionnaire
ET	Early termination
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HP	Halobetasol propionate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
ITT	Intent-to-treat
LOCF	Last observation carried forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Affairs
PP	Per protocol
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event

In this protocol, “sponsor duties” refer to responsibilities that will be performed by the sponsor, the sponsor’s designee, or the sponsor’s designated contract research organization. In this protocol, “investigator” refers to the principal investigator or his/her designee, who is responsible for performing the study procedures and assessments.

## 5 Introduction

Psoriasis is a chronic, immune-mediated disease that varies widely in its clinical expression. Disease severity ranges from mild (limited number of plaques) to very severe. Characteristic features of psoriasis include hyperproliferation of epidermal cells associated with dermal/epidermal inflammation, resulting in sharply demarcated red plaques, which may be covered by silvery scales affecting the skin and scalp.

There are presently no curative treatments for psoriasis. Treatment options focus on relieving symptoms, reducing inflammation, induration, and scaling, and controlling the extent of the disease. Patient age, severity of disease, and the type and extent of body surface area (BSA) involvement are considerations in selecting therapy.

Biologic treatments are now either available or in development to treat psoriasis. However, these treatments are not typically used for mild disease, and their safety profile is not entirely well understood.

Topical therapies are used in all disease severities, but may be impractical when psoriasis involves a large BSA. The mainstay of psoriasis treatment is topical corticosteroids, which range in potency from superpotent to low potency (Class I to Class VII, respectively). Generally, the more potent corticosteroids are required for effective management of psoriasis.

Although topical corticosteroids are very effective, long-term safety remains a concern, particularly with the more potent ones. Adverse effects such as skin atrophy, telangiectasia, and potential hypothalamic-pituitary-adrenal axis suppression have been associated with higher potency topical corticosteroids and prolonged treatment. Ultravate<sup>®</sup> cream and ointment (halobetasol propionate [HP] 0.05%) is currently on the market and are classified as super-high potency (Class I) corticosteroids indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Having a lower concentration product that is a Class I steroid might be advantageous for patients, as the steroid provides relief from inflammation, and may reduce the adverse reactions associated with a steroid (eg, skin atrophy).

## 6 Study Objectives and Purpose

The objective of the study is to evaluate the safety and efficacy of topical IDP-122 Lotion when applied once daily to adult subjects with moderate to severe plaque psoriasis (defined as an Investigator's Global Assessment [IGA] score of 3 or 4). The intent of the study is specifically to evaluate the safety and efficacy of a once daily application of IDP-122 Lotion in comparison with vehicle.

## 7 Investigational plan

### 7.1 Overall Study Design and Plan: Description

This is a multicenter, double-blind, randomized, parallel-group study designed to assess the safety and efficacy of IDP-122 Lotion in comparison with its vehicle. To be eligible for the study, subjects must be at least 18 years of age and have a clinical diagnosis of moderate to severe psoriasis (defined as an IGA score of 3 or 4).

Approximately 210 subjects who meet the study entry criteria will be randomized in a 2:1 ratio to receive IDP-122 (HP 0.01%) Lotion and IDP-122 Vehicle Lotion, respectively. The assigned study drug will be applied topically to the affected area (as determined by the investigator at Baseline) once daily for 8 weeks. The initial application will be made at the investigational center during the day as per instruction from the study coordinator or designee. The subjects will be instructed to avoid exposure to direct sunlight, artificial ultraviolet light sources and to use protective clothing to prevent sunburn. Subjects will apply their daily treatments at home as explained by the study coordinator or designee at each investigational center. The study coordinator or designee at each investigational center will dispense 2 new containers of study drug to each subject at Baseline and Weeks 2, 4, and 6. During post-baseline study visits (Weeks 2, 4, 6, and 8) the subjects will be asked to return their used containers of study drug. Subjects will be asked to not apply study drug on day of clinic visit so that subject can apply during the visit after assessments are completed. Upon completion of the 8-week treatment period, all subjects will be asked to return to the investigational center 4 weeks later for a post-treatment cessation follow-up visit (Week 12). During the study, each subject will only be permitted to use Investigator approved non-medicated cleansers, moisturizers and sunscreens; no other skin care products will be permitted on the treatment areas.

The investigator will assess the treatable areas affected by psoriasis at each study visit. All treatable areas affected by psoriasis identified at Baseline (with an affected BSA of 3%-12%) are to be treated with study drug. The treatable affected areas will not include the face, scalp, palms, soles, axillae, and intertriginous areas. If palms and soles are affected, study drug may be applied at the discretion of the investigator; however, these areas will not be included in treatable BSA or efficacy assessments.

Information on reported and observed adverse events (AEs) will be obtained at each visit. An abbreviated physical examination will be performed at Baseline, Week 8 (end of treatment), and Week 12 (the 4-week post-treatment cessation follow-up visit) for all subjects.

Blood samples for complete blood count with differential (CBC/Diff) and serum chemistry will be collected from subjects at Screening, Week 4, and Week 8. For all female subjects of childbearing potential, urine and serum pregnancy testing will be performed at Screening and confirmed at baseline with a urine pregnancy test prior to randomization. Serum pregnancy tests will also be conducted at weeks 4 and 8, and an additional urine pregnancy test will be performed at Week 12 (4-week post-treatment follow-up visit).

The Dermatology Life Quality Index questionnaire (DLQI) questionnaire will be administered to subjects at Day 0 (Baseline), Week 4, Week 8/End of Treatment and Week 12 (4-week post-treatment follow-up visit).

Subjects who terminate study participation early will be asked to complete all Week 8 assessments, as appropriate, prior to commencement of any alternative therapy for psoriasis (if possible). Subjects who discontinue from the study during the treatment period will not be replaced and these subjects may be asked to come back for the 4-week post-treatment cessation follow-up visit.

**Table 1. Study Design and Schedule of Assessments**

<b>PROCEDURES</b>	<b>-Day -35 to -1 Screening</b>	<b>Day 0 Baseline</b>	<b>Week 2 (14 ± 3 days)</b>	<b>Week 4 (28 ± 3 days)</b>	<b>Week 6 (42 ± 3 days)</b>	<b>Week 8/ET<sup>a</sup> (56 ± 5 days)</b>	<b>Week 12/FU (Day 84 ± 7 days)</b>
Informed consent	X						
Demographics	X						
Medical history <sup>b</sup>	X	X					
Previous psoriasis therapies <sup>b</sup>	X	X					
Inclusion/Exclusion criteria <sup>b</sup>	X	X					
Abbreviated physical examination <sup>c</sup>		X				X	X
Pregnancy testing <sup>d</sup>	X	X		X		X	X
Clinical laboratory tests <sup>e</sup>	X			X		X	
DLQI questionnaire		X		X		X	X
Investigator's Global Assessment	X	X	X	X	X	X	X
Psoriasis Signs Assessment (Target Lesion)	X	X	X	X	X	X	X
Photography (Target Lesion + 1 other selected Lesion)		X	X	X	X	X	X
Body surface area (BSA) affected evaluation	X	X	X	X	X	X	X
Local skin reactions evaluation		X	X	X	X	X	X
Randomization		X					
Review study drug application instructions		X	X	X	X		
Study drug weighed and dispensed		X	X	X	X		
Study drug collected and weighed			X	X	X	X	
Study diary calendar dispensed		X	X	X	X		
Review compliance with dosing / Diary			X	X	X	X	
Review adverse events		X	X	X	X	X	X
Review concomitant therapies	X	X	X	X	X	X	X
Study exit/end of study form							X

ET = early termination; FU = follow-up

<sup>a</sup> For subjects who discontinue early during the treatment period, all procedures outlined for the ET visit should be completed at the time of discontinuation or within 2 weeks of discontinuation.

<sup>b</sup> Update at Day 0 (Baseline).

<sup>c</sup> Height will be measured at Baseline only; vital signs, weight measurements and examinations of other abbreviated physical parameters will be performed at Baseline, Week 8, and Week 12.

<sup>d</sup> All female subjects of childbearing potential will undergo serum pregnancy testing at Screening, Week 4, and Week 8. In addition, urine pregnancy testing will be performed at Screening, Baseline (prior to randomization), and Week 12 (4-week post-treatment follow-up visit).

<sup>e</sup> Blood samples for laboratory tests will be collected at Screening prior to study drug application. Clinically significant laboratory findings at Week 4 or Week 8 will be repeated at the discretion of the investigator, and the subject will be followed until resolution (return to normal or to the baseline state) or until clinically stable as determined by the investigator.

## 8 Selection and Withdrawal of Subjects

### 8.1 Subject Inclusion Criteria

Subjects meeting all of the following criteria will be eligible for study entry:

1. Male or female, of any race, at least 18 years of age.
2. Freely provides both verbal and written informed consent.
3. Has an area of plaque psoriasis appropriate for topical treatment that covers a (BSA) of at least 3%, but no more than 12%. The face, scalp, palms, soles, axillae, and intertriginous areas are to be excluded in this calculation.
4. Has a clinical diagnosis of psoriasis at the Baseline visit with an IGA score of 3 or 4 (the face, scalp, palms, soles, axillae and intertriginous areas are to be excluded in this calculation, if psoriasis is present).
5. Has a target lesion that meets the following criteria:
  - Measures between 16-100 cm<sup>2</sup> inclusive
  - A score of at least 3 for at least 2 of the 3 different psoriasis signs (erythema, plaque elevation, and scaling); with a sum of the three scores at least eight (8) and cannot have a score of 0 or 1 on any one of the signs
  - Target lesions cannot be on excluded areas or areas covering bony prominences (i.e., elbows and knees)
6. Is in good general health based on the subject's medical history and a physical examination, with Screening hematology, and serum chemistry laboratory values within normal range or not clinically significant as determined by the investigator.
7. If female and of childbearing potential, must have a negative urine and serum pregnancy test at Screening and negative urine pregnancy test at Baseline prior to randomization.
8. If female, is either not of childbearing potential, defined as postmenopausal for at least 12 months or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or is of childbearing potential and practicing 1 of the following methods of birth control throughout the study:
  - Condom with spermicide, diaphragm with spermicide, intrauterine device, or abstinence
  - Stable use of a hormonal contraceptive (oral, implant, insertable, injection or transdermal patch) for at least 3 months prior to the Baseline visit
9. Subject is willing to comply with study instructions and return to the clinic for required visits



## 8.2 Subject Exclusion Criteria

Subjects meeting any 1 of the following criteria will be excluded from the study:

1. Has spontaneously improving or rapidly deteriorating plaque psoriasis or pustular psoriasis, as determined by the investigator.
2. Presents with psoriasis that was treated with prescription medication and failed to respond to treatment, even partially or temporarily, as determined by the investigator.
3. Presents with any concurrent skin condition that could interfere with the evaluation of the treatment areas, as determined by the investigator.
4. Is pregnant, nursing an infant, or planning a pregnancy during the study period.
5. Has received treatment with any investigational drug or device within 60 days or 5 drug half-lives (whichever is longer) prior to the Baseline visit, or is concurrently participating in another clinical study with an investigational drug or device.
6. Received treatment with any topical antipsoriatic drug product within 14 days prior to the Baseline visit.
7. Has used any phototherapy (including laser), photochemotherapy, or non-biologic systemic psoriasis therapy (such as newer oral psoriasis medications (eg Otezla), systemic corticosteroids, methotrexate, retinoids, or cyclosporine) within 4 weeks prior to the Baseline visit.
8. Has used immunomodulatory therapy (biologics) known to affect psoriasis within 3 months of the Baseline visit.
9. Has had prolonged exposure to natural or artificial sources of ultraviolet radiation within 4 weeks prior to the Screening visit or is intending to have exposure during the study thought likely by the investigator to modify the subject's psoriasis.
10. Is currently using lithium or Plaquenil.
11. Has a history of hypersensitivity or allergic reaction to any of the study drug constituents.
12. Is unable to be compliant with study procedures, study drug administration requirements, study visit schedules, and prohibitions regarding the use of concomitant medications/therapies.
13. Is unable to communicate or cooperate with the investigator.
14. Has any underlying disease (eg, uncontrolled diabetes, cardiac disease) that the investigator deems uncontrolled that poses a concern for the subject's safety while participating on the study.
15. Has a history of drug or alcohol abuse.
16. Is considered by the investigator, for any other reason, to be an unsuitable candidate for the study.

### 8.3 Subject Withdrawal Criteria

Reasons for withdrawal may include, but are not limited to, the following:

- Psoriasis flare, as determined by the investigator, which requires treatment with a disallowed therapy.
- Either at the investigator's request, for tolerability reasons (e.g., severe adverse reactions), or at the subject's request.
- When the requirements of the protocol are not followed.
- When a concomitant therapy likely to interfere with the results of the study is reported, or required by the subject (the investigators will report all such information on the source documents/electronic case report forms (eCRFs) and decide, in accordance with the sponsor, whether the subject is to be withdrawn).
- When a subject is lost to follow-up. The investigators will try twice to reach the subject by telephone and will send a follow-up letter by certified mail before considering that the subject is lost to follow-up. These actions will be reported on the End of Study eCRF and a copy of the follow-up letter maintained in the investigator's file.

All premature discontinuations and their reasons must be carefully documented by the investigator on the final eCRF, and, if need be, on the AE form. In any case, no subject who has been included and has a study number assigned can be replaced by another if they discontinue prematurely for whatever reason. All data gathered on the subject prior to termination will be made available to the sponsor.

Reasons for study completion/discontinuation as listed on the final report form are defined as follows:

**Normal Study Completion** – Subject completes the study as planned in the protocol.

**Adverse Event** – Complete AE form.

**Subject Request** – Consent withdrawal, subject moved, schedule conflicts.

**Protocol Violation** – Contact the Sponsor or designee before making decision.

**Lost to Follow-Up** – Document with 2 phone calls and a certified letter.

**Pregnancy** – Subject will discontinue study drug immediately, but will be followed to term. Complete pregnancy form.

**Worsening Condition** – Subject requires alternate treatment for psoriasis before the end of the study and the investigator determines it is not due to lack of efficacy.

**Lack of Efficacy** – Subject requires alternate treatment for psoriasis after at least 2 weeks of study drug treatment and the risk of continuing the subject in the study outweighs the benefit as determined by the investigator.

**Other** – Specify in comments section of final eCRF.

Subjects who terminate treatment early will be asked to complete all Week 8 assessments prior to commencement of any alternative therapy for psoriasis (if possible). Subjects who discontinue from the study during the treatment period will not be replaced and these subjects will be asked to come back for the 4-week post-treatment cessation follow-up visit.

All subjects are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, and without prejudice. No constraints will be placed on ordinary subject management, and subjects, when appropriate, will be placed on other conventional therapy upon request or whenever clinically necessary as determined by their physician.

## **9 Treatment Plan**

### **9.1 Methods of Assigning Subjects to Treatment Groups**

This is a double-blinded study, in which the identity of the study drug will be unknown to investigator/evaluator and subjects, as well as all individuals closely associated with the study.

Subjects will be randomized to 1 of the 2 study drug groups in a ratio of 2:1 (IDP-122 [HP 0.01%] Lotion: IDP-122 Vehicle Lotion). Each screened subject will be assigned a unique 6-digit study subject number assigned by the investigational center, which will consist of the 3-digit investigational center/site number (pre-assigned by sponsor/designee) and the 3-digit chronological screening order number, starting with 001 (e.g., 101001, 101002). The study drug kit will be assigned to subjects based on a randomization code and kits will be dispensed to the subjects at Baseline. A study drug log will document the inventory and dispensing of study drug at each investigational center.

### **9.2 Randomization and Blinding**

The study drugs will be packaged and labeled identically, and the study drug kits will be numbered sequentially and dispensed randomly to the subjects entering the study within each investigational center. Study drug supplies will be distributed to the investigational centers to maintain the randomization ratio within each investigational center.

As a double-blinded study, the investigators, the site staff, the sponsor, and the clinical monitors will not be aware of the treatment assigned to the individual study subjects. Delegated staff members at each investigational center will dispense the study drugs and will collect all used and unused study drug containers as scheduled.

### 9.3 Unblinding

The treatment assignments for all enrolled subjects will be unblinded only after the conclusion of the study. Specifically, the blind will be broken only after all data are verified, entered into the database, and validated; subject evaluability assessments are performed and entered into the database; and the database is locked.

In the case of a medical emergency, the investigator can break the blind for the subject involved preferably by first discussing the situation with the medical monitor and the sponsor (or designee) immediately. After confirmation, the investigator will be contacted with unblinding information by a sponsor representative. The investigator will record the code break in the subject's source documents.

### 9.4 Prior and Prohibited Concomitant Medication or Therapy

Subjects in this study must not have psoriasis that was previously nonresponsive to prescription medications, per the Investigators' best clinical judgment. Subjects must also not be using lithium or Plaquenil. Any concomitant therapy stopped for washout as indicated below is to be recorded. As noted in the exclusion criteria, there are mandatory washout periods and restrictions during the study. Specifically:

- Received treatment with any topical antipsoriatic drug product within 14 days prior to the Baseline visit
- Within 4 weeks prior to the Baseline visit, subjects must not have used any phototherapy (including laser), photochemotherapy, or non-biologic systemic psoriasis therapy (such as newer oral psoriasis medications (eg Otezla), systemic corticosteroids, methotrexate, retinoids or cyclosporine)
- Has used immunomodulatory therapy (biologics) known to affect psoriasis within 3 months of the Baseline visit
- Within 4 weeks prior to the Baseline visit, subjects must not have had prolonged exposure to natural or artificial sources of ultraviolet radiation
- Within 60 days or 5 drug half-lives (whichever is longer) prior to the Baseline visit, subjects must not have received treatment with any investigational drug or device and may not be concurrently participating in another clinical study with an investigational drug or device

Subjects are allowed only the use of investigator approved non-medicated cleansers, moisturizers, and sunscreens in the treatment areas. Protocol excluded areas (face, scalp, axillae, and intertriginous areas) may be treated with OTC 1% hydrocortisone cream, tar shampoos or allowed moisturizers.

Protocol excluded areas of palms and soles may be treated with study drug but will not be included in the BSA or IGA assessments. If palms and soles are treated, they may be evaluated by the investigator for improvement.

Subjects using concomitant therapies during the course of the study that could interfere with the interpretation of the study results (including but not limited to those listed above) should not be withdrawn, but the use of the concomitant product should be discontinued. No other topical treatment (except as noted above) other than the study drug will be permitted for psoriasis.

Information on concomitant therapies will be recorded in the Prior and Concomitant Medication or Therapy source document. Any therapy used by the subject will be considered concomitant medication or therapy (e.g., aspirin, Tylenol, birth control pills, vitamins, moisturizers, sunscreens). Every attempt should be made to keep concomitant therapy dosing constant during the study. Any change to concomitant therapy should be noted on the Concomitant Therapy source document and eCRF.

### **9.5 Treatment Compliance**

Each subject will be instructed on the importance of returning his or her study drug at each applicable study visit. If a subject does not return his or her study drug, he or she will be instructed to return it as soon as possible. The subjects will bring the containers dispensed at each on-site treatment visit to the next subsequent study visit. The maximum allowable weekly usage is 50 grams for this study. Each container will be weighed by a study coordinator or designee prior to dispensation and after collection. The subject will also be asked to complete a diary calendar and questioned regarding the study drug use since the previous visit in order to judge the subject's compliance with applying the study drug. A subject who deviates significantly from the prescribed application amount will be counseled. Any missed applications of study drug will be noted by subject on the diary, which will be collected and placed in the appropriate source document. Missed applications will be documented in the eCRF.

### **9.6 Protocol Deviations and Violations**

The investigators must read the protocol thoroughly and must follow the instructions exactly. A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria.

A protocol violation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the patient, when the patient or investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria) and the patient was enrolled without prior sponsor approval, or when there is nonadherence to FDA regulations and/or ICH GCP guideline.

The investigator or designee must document and explain in the patients' source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

## **10 Study Drug Materials and Management**

The study drug will be dispensed by an appropriately qualified member of the study staff assigned by the investigator to this task

### **10.1 IDP-122 Lotion and IDP 122 Vehicle Lotion**

The study drug contains the following ingredients: HP, diethyl sebacate, light mineral oil, sorbitan monooleate, sorbitol, disodium edetate dihydrate, Pemulen TR-1, Carbopol 981, methylparaben, propylparaben, sodium hydroxide, and purified water.

The vehicle contains the following ingredients: Diethyl sebacate, light mineral oil, sorbitan monooleate, sorbitol, disodium edetate dihydrate, Pemulen TR-1, Carbopol 981, methylparaben, propylparaben, sodium hydroxide, and purified water.

#### **10.1.1 Packaging and Labeling**

IDP-122 Lotion and IDP-122 Vehicle Lotion will be packaged in identical study drug kits. Each kit will contain 2 containers (tubes), each containing 45 grams of study material. The subjects will be dispensed both containers at Baseline as assigned by the IRT system. The containers will be weighed prior to dispensing. The subject will bring the containers to the next study visit, where they will be collected and weighed; 2 new containers will be dispensed again by the IRT system, weighed and provided to the subject at each on treatment study visit. If the subject loses a container (lost or damaged tube), another kit will be dispensed via IRT. Each drug container dispensing will be documented on the drug accountability log.

Labels on the containers will contain the following information:

- Protocol Number
- Subject Number
- Space for entry of the subject initials
- Space for entry of date dispensed
- A statement reading, “For external use only. Avoid contact with eyes and lips”
- A statement reading, “Store at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F)”
- A statement indicating the sponsor, Dow Pharmaceutical Sciences, a Division of Valeant Pharmaceuticals North America LLC
- A statement indicating the quantity of product (45 grams)
- A statement reading, “Caution: New Drug Limited by Federal Law to Investigational Use”
- A statement reading, “Keep out of Reach of Children”

### **10.1.2 Storage, Handling, and Disposal of Study Drug**

The study drug should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F).

### **10.1.3 Administration**

The investigational center staff member will instruct the subject on the proper application procedure of the study drug to the affected treatment areas identified at the Baseline visit by the investigator. Subjects will be instructed to squeeze a small amount of study drug (about the size of a pea) onto a fingertip and then spread a thin layer of the study drug over the affected treatment area. If necessary, additional pea-sized amounts of study drug may be applied in increments to cover all affected treatment areas as designated by the investigator. The maximum allowable weekly usage is 50 grams for this study. In addition to the verbal instructions given during the visit, the subjects will be provided with written instructions (See [Appendix 17.1](#)).

Subjects will be instructed to apply a thin layer of study drug to the entire selected treatment area(s), as indicated on the body diagram. Subjects will be advised to avoid or minimize exposure to direct sunlight and artificial ultraviolet light sources while in the study and to wash their hands before and after application of the study drug.

It is suggested that subjects do not apply study drug on day of clinic visits so that this may be done by the subject at the clinic after study assessments are completed and to confirm proper application technique and retrain as necessary.

## **10.2 Study Drug Accountability**

Upon receipt of the study drug, the investigator is responsible for ensuring that the investigational center staff member will conduct a complete inventory of study materials and assume responsibility for their storage and dispensing. In accordance with federal regulations, the investigators must agree to keep all study materials in a secure location with restricted access. The investigator will keep a record of the inventory and dispensing of all study drug. This record will be made available to the sponsor's monitor for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the investigators will be accounted for and, in no case, used in any unauthorized situation. Each tube will be weighed (with the cap on) before dispensing to and upon return by the subjects, and weights will be recorded on the pharmacy log and appropriate eCRF. All used and unused supplies will be returned to the sponsor/designee for destruction at the conclusion of the study.

## **11 Study Procedures and Evaluations**

All subject information and data obtained during the study visits will be recorded in the source documents, applicable study logs, and eCRFs.

Evaluators must have appropriate, documented experience and training, or obtain approval from the sponsor based on experience (or through additional training organized by the sponsor).

At each study visit, every attempt should be made to ensure that the same investigator/evaluator assesses the same subject.

### **11.1 Schedule of Evaluations and Procedures**

#### **11.1.1 Screening Visit (Day -35 to Day -1)**

The following procedures will be conducted at this visit:

1. Obtain verbal and written informed consent from the subject prior to performing any study related procedures. Give a signed copy to the subject.
2. Review and explain the nature of the study. Provide a visit schedule with the length of each visit to ensure subject can meet the requirements and has adequate transportation.



3. Assign the subject a 6-digit subject number by accessing IRT, which will consist of the 3-digit site number (pre-assigned to your site) and the 3-digit chronological order screening number, assigned by the IRT system and starting with 001 (e.g., 101001, 101002, etc.; in this example site number is 101).
4. Record the subject's demographic information.
5. Record the subject's medical history.
6. Record all previous medications for psoriasis used during the past 6 months under Prior and Concomitant Medications or Therapies. Include all medications used in the past 30 days and any therapy that requires a washout prior to Baseline.
7. Record any prescription or over-the-counter therapies that are being used concomitantly under Prior and Concomitant Medications or Therapies. All medications taken within 30 days of the Screening visit should be recorded including any that may have ended prior to the Screening visit.
8. Record all previous cleansers, moisturizers, etc. in the past 30 days under Prior and Concomitant Medications or Therapies. Inform subjects that only Investigator-approved non-medicated cleansers, moisturizers, and sunscreens are allowed.
9. The investigator will assess the BSA affected by psoriasis and determine whether the locations of plaques are treatable with the study drug. The face, scalp, palms, soles, axillary areas, and other intertriginous areas will not count towards the total treatable BSA calculation.
10. The investigator/evaluator will conduct the IGA for the disease severity of the treatment areas. The face, scalp, palms, soles, axillary areas and other intertriginous areas will not be included in the severity score using the IGA scale. Every attempt should be made for the same sponsor-approved, qualified evaluator to perform the evaluations for the same subject.
11. The investigator/evaluator will select a target lesion measuring between 16-100 cm<sup>2</sup> inclusive. Target lesion cannot be on excluded areas or areas covering bony prominences (i.e., elbows and knees).
12. The investigator/evaluator will assess the signs of psoriasis (erythema, plaque elevation, and scaling) of the selected target lesion.
13. For female subjects of childbearing potential collect a urine sample for a urine pregnancy test.
14. Verify that the subject meets the applicable inclusion/exclusion criteria as outlined in [Sections 8.1](#) and [8.2](#).
15. Discuss the use of acceptable cleansers and moisturizers (only products approved by the investigator for this study will be allowed) with the subject.
16. Collect blood samples for routine laboratory analysis (CBC/Diff and serum chemistry and for remales subjects of childbearing potential serum pregnancy).

17. Schedule subject to return for the Baseline/Day 0 visit. If the subject requires a washout, schedule the Baseline/Day 0 visit to occur after the washout is complete.

**NOTE:** At the Screening, Weeks 4, and 8 visits, serum pregnancy testing is **mandatory** for all females of childbearing potential. In addition, a urine pregnancy test must be completed at Screening and at the Baseline visit prior to randomization, and at Week 12. The decision may be made by the investigator to do additional pregnancy tests during the course of the study.

#### 11.1.2 Baseline Visit (Day 0)

The following procedures will be conducted at this visit:

1. Record any changes in medical history since Screening.
2. Record changes in any previous psoriasis medications since the previous visit under Prior and Concomitant Medications or Therapies. Check for prohibited concomitant therapies and confirm any therapy that requires a washout prior to Baseline as per [Section 9.4](#).
3. Record changes in any concomitant medications since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant therapies as per [Section 9.4](#).
4. Record changes in cleansers, moisturizers and sunscreens since the previous visit under Prior and Concomitant Medications or Therapies. Remind subjects that only Investigator-approved non-medicated cleansers, moisturizers and sunscreens are allowed.
5. Verify that the subject continues to meet the applicable inclusion/exclusion criteria as outlined in [Sections 8.1](#) and [8.2](#).
6. For female subjects of child bearing potential, perform a urine pregnancy test prior to randomization. The pregnancy test must be negative for the subject to be eligible for randomization.
7. Provide subject with DLQI for completion.
8. The investigator will perform an abbreviated physical examination including measurements of height, weight, and vital signs (blood pressure, heart rate, respiration rate, and oral temperature).
9. The investigator will determine the extent of psoriasis, i.e., percent of body surface area (BSA) involvement in the selected treatment areas. The face, scalp, palms, soles, axillary areas, and other intertriginous areas will not count towards the total treatable BSA calculation.
10. The investigator/evaluator will conduct the IGA for the disease severity of the treatment area. The face, scalp, palms, soles, axillary areas, and other intertriginous areas will not count towards the IGA severity score. Every attempt should be made for the same sponsor-approved, qualified evaluator to perform the evaluations for the same subject.

11. The investigator/evaluator will select a target lesion measuring between 16-100 cm<sup>2</sup> inclusive. Target lesion cannot be on excluded areas or areas covering bony prominences (i.e., elbows and knees).
12. Take photographs of selected target lesion and choose one other lesion to photograph. The selected lesions should be photographed consistently for all subsequent visits.
13. The investigator/evaluator will assess the signs of psoriasis (erythema, plaque elevation, and scaling) of the selected target lesion.
14. The investigator/evaluator will evaluate local skin reactions (itching, dryness, burning/stinging, skin atrophy, striae, telangiectasia and folliculitis) by observation and questioning the subjects as necessary.
15. Randomize the subject using the IRT system and record the assigned kit number in the source document and in the eCRF.
16. The study coordinator or designee will weigh each tube within the assigned kit and dispense them to the subject. A study diary calendar will also be dispensed.
17. The study coordinator or designee will instruct the subject on the proper application procedure for the study drug. For the first application, the subject will apply the study drug at the investigational center during the day under the direction of the study coordinator or designee. The study drug should be applied **after** all clinical assessments. The subjects will be asked to avoid exposure to direct sunlight and artificial ultraviolet light sources on the initial application day and thereafter. The study coordinator or designee will instruct the subjects to apply the study drug once daily at home.
18. Record any AEs reported spontaneously by the subject.
19. Schedule the next study visit at Week 2 (Day 14 ± 3 days).

#### **11.1.3 Week 2 (Day 14 ± 3 Days), Week 4 (Day 28 ± 3 Days), Week 6 (Day 42 ± 3 Days) Visits**

The following procedures will be conducted at this visit:

1. Record changes in any concomitant medications since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant therapies as per [Section 9.4](#).
2. Record changes in cleansers, moisturizers and sunscreens since the previous visit under Prior and Concomitant Medications or Therapies. Remind subjects that only investigator approved non-medicated cleansers, moisturizers and sunscreens are allowed.
3. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
4. The investigator will determine the percent BSA affected by Psoriasis.

5. The investigator/evaluator will conduct the IGA for the disease severity of the treatment area. The face, scalp, palms, soles, axillary areas, and other intertriginous areas will not count towards the IGA severity score. Every attempt should be made for the same sponsor-approved, qualified evaluator to perform the evaluations for the same subject.
6. The investigator/evaluator will assess the signs of psoriasis (erythema, plaque elevation, and scaling) on the selected Target Lesion
7. Take photographs of the same lesions selected by the investigator for Photography.
8. The investigator/evaluator will evaluate local skin reactions (itching, dryness, burning/stinging, skin atrophy, striae, telangiectasia and folliculitis) by observation and questioning the subjects as necessary.
9. **At Week 4**, collect blood samples for routine laboratory analysis (CBC/Diff, serum chemistry, and for women of child bearing potential a serum pregnancy test).
10. **At Week 4**, provide subject with DLQI for completion.
11. The study coordinator or designee will collect and weigh the previously dispensed study drug tubes. The study coordinator or designee will weigh and dispense 2 new study drug tubes from the next IRT-assigned kit to the subject.
12. The study diary calendar will be collected and reviewed for compliance. Any missed doses or deviations should be reported. A new study diary calendar will be dispensed.
13. The study coordinator or designee will remind the subject of the proper technique for application of the study drug. Preferably, the subject can apply the study drug at the investigational center during the day under the direction of the study coordinator or designee to confirm proper technique. Any necessary retraining can be completed. The study drug should be applied after all clinical assessments.
14. Schedule the subsequent study visit, as applicable.

#### **11.1.4 Week 8 (Day 56 ± 5 Days) End of Treatment – Perform these Visit Procedures for Subjects who Discontinue Treatment Early**

The following procedures will be conducted at this visit:

1. Record changes in any concomitant medications since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant therapies as per [Section 9.4](#).
2. Record changes in cleansers, moisturizers and sunscreens since the previous visit under Prior and Concomitant Medications or Therapies. Remind subjects that only investigator approved non-medicated cleansers, moisturizers and sunscreens are allowed.
3. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
4. The investigator will determine the percent BSA affected by Psoriasis.

5. The investigator/evaluator will conduct the IGA for the disease severity of the treatment area. The face, scalp, palms, soles, axillary areas, and other intertriginous areas will not count towards the IGA severity score. Every attempt should be made for the same sponsor-approved, qualified evaluator to perform the evaluations for the same subject.
6. The investigator/evaluator will assess the signs of psoriasis (erythema, plaque elevation, and scaling) on the selected Target Lesion
7. Take photographs of the same lesions selected by the investigator for Photography.
8. The investigator/evaluator will evaluate local skin reactions (itching, dryness, burning/stinging, skin atrophy, striae, telangiectasia and folliculitis) by observation and questioning the subjects as necessary.
9. The investigator will perform an abbreviated physical examination including measurements of weight and vital signs (blood pressure, heart rate, respiration rate, and oral temperature).
10. Collect blood samples for routine laboratory analysis (CBC/Diff and serum chemistry).
11. For women of child bearing potential, collect a blood sample for a serum pregnancy test.
12. Provide subject with DLQI for completion.
13. The study coordinator or designee will collect all previously dispensed study drug tubes (used and unused) and weigh all collected tubes.
14. The study diary calendar will be collected and reviewed for compliance. Any missed doses or deviations should be reported.
15. Schedule the 4-week post-treatment follow-up visit to occur on Day 84 ( $\pm 7$  days).

**Note:** For subjects who exit the study prior to completing Week 8, perform all of the assessments scheduled for Week 8 at the time that the subject discontinues or within 2 weeks of subject discontinuation. The subject will be asked to come back for the 4-week post-treatment cessation follow-up visit.

#### **11.1.5 Week 12 (Day 84 $\pm$ 7 Days) – 4-Week Post-Treatment Cessation Follow-Up Visit**

The following procedures will be conducted at this visit:

1. Record changes in any concomitant medications since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant therapies as per [Section 9.4](#).
2. Record changes in cleansers, moisturizers and sunscreens since the previous visit under Prior and Concomitant Medications or Therapies. Remind subjects that only investigator approved non-medicated cleansers, moisturizers and sunscreens are allowed.

3. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
4. The investigator will determine the percent BSA affected by Psoriasis.
5. The investigator/evaluator will conduct the IGA for the disease severity of the treatment area. The face, scalp, palms, soles, axillary areas, and other intertriginous areas will not count towards the severity score using the IGA scale. Every attempt should be made for the same sponsor-approved, qualified evaluator to perform the evaluations for the same subject.
6. The investigator/evaluator will assess the signs of psoriasis (erythema, plaque elevation, and scaling) on the selected Target Lesion.
7. Take photographs of the same lesions selected by the investigator for Photography.
8. The investigator/evaluator will evaluate local skin reactions (itching, dryness, burning/stinging, skin atrophy, striae, telangiectasia and folliculitis) by observation and questioning the subjects as necessary.
9. The investigator will perform an abbreviated physical examination including measurements of weight and vital signs (blood pressure, heart rate, respiration rate, and oral temperature).
10. For women of child bearing potential, perform a urine pregnancy test.
11. Provide subject with DLQI for completion.
12. Exit the subject from the study and complete the end of study eCRFs.

**Note:** For subjects, who exit the study after Week 8 but prior to completing Week 12, perform all of the assessments scheduled for Week 12 at the time that the subject discontinues or within 2 weeks of subject discontinuation.

## **11.2 Evaluation of Efficacy**

### **11.2.1 Body Surface Area Affected by Psoriasis (BSA)**

The investigator will assess the percent BSA (3%-12% required to qualify at Baseline) affected by psoriasis in the allowed treatment areas for each subject at Screening/Baseline and at all study visits. The BSA will not include areas of the face, scalp, palms, soles, axillae, and other intertriginous areas. Note: palms and soles with psoriasis may be treated with the study drug but will not be included in the BSA or IGA assessments.

### **11.2.2 Investigator's Global Assessment (IGA)**

The IGA is based on a 5-point scale ranging from 0 (clear) to 4 (severe), and will be assessed by the evaluator at each visit for the overall affected areas with plaque psoriasis. The face, scalp, palms, soles, axillae, and intertriginous areas are to be excluded in this assessment.

The scores to be used to describe the severity of overall psoriasis of the treatable areas are shown in Table 2.

**Table 2. Investigator's Global Assessment Scale**

<b>Grade</b>	<b>Score</b>	<b>Description</b>
Clear	0	No evidence of scaling; No evidence of erythema; No evidence of plaque elevation above normal skin level
Almost Clear	1	Some plaques with fine scales; Faint pink/light red erythema on most plaques; Slight or barely perceptible elevation of plaques above normal skin level
Mild	2	Most to all plaques have some fine scales but are not fully covered, some plaques are completely covered with fine scale; Most to all plaques are pink/light red to bright red in color; Some plaques have definite elevation above normal skin level, typically with edges that are indistinct and sloped on some of the plaques
Moderate	3	Some plaques are at least partially covered with a coarse scale, most to all plaques are nearly covered with fine or course scale; Most to all plaques are bright red, some plaque may be dark red in color; Definite elevation of most to all plaques; rounded or sloped edges on most of the plaques
Severe	4	Most to all plaques are covered with coarse, thick scales; Most or all plaques are bright, dark or dusky red; Almost all plaques are raised and well-demarcated; sharp edges on virtually all plaques

### 11.2.3 Psoriasis Signs

The signs of psoriasis (erythema, plaque elevation, and scaling) will be assessed using the following scales for the selected target lesion shown in Table 3.

**Table 3. Psoriasis Signs**

Score	Grade	Description
<i>Erythema:</i>		
0	None	No erythema
1	Minimum	Pink discoloration, minimal erythema
2	Mild	Most plaques are light red to red in color
3	Moderate	Most or all plaques are bright red or dark red in color
4	Severe	Most plaques dusky red with purple hue
<i>Plaque Elevation:</i>		
0	None	No evidence elevation above the normal skin level
1	Minimum	Slight, just discernible elevation above normal skin level
2	Mild	Some plaques show definite elevation with indistinct edges
3	Moderate	Most plaques have definite elevation with distinct edges that are rounded or sloped
4	Severe	Almost all plaques are raised above normal skin level with sharp edges
<i>Scaling:</i>		
0	None	No scales on very few plaques
1	Minimum	Occasional fine scales hardly noticeable
2	Mild	Most plaques have fine scales
3	Moderate	Some plaques have coarse scales while most plaques have fine scales
4	Severe	Most plaques are covered by thick coarse scales

## 11.3 Evaluation of Safety

### 11.3.1 Localized Skin Reactions

Tolerability will be evaluated through assessments of selected local signs and symptoms (itching, dryness, and burning /stinging). In addition, the treatment areas will be examined by the evaluator at each visit for presence or absence of significant known drug-related AEs; skin atrophy, striae, telangiectasia, and folliculitis. Any local skin reaction requiring use of a concomitant therapy or is a cause for study drug interruption or discontinuation should be reported as an adverse event. The scales to be used for assessing local skin reactions are shown in



**Table 4. Localized Skin Reaction Scales**

Score	Grade	Description
<i>Itching: as reported by the subject within the last 24 hours</i>		
0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching that is somewhat bothersome
3	Severe	Intense itching that may interrupt daily activities and/or sleep
<i>Dryness: as assessed by the investigator</i>		
0	None	No dryness
1	Mild	Slight, but definite roughness
2	Moderate	Definite roughness
3	Severe	Marked roughness
<i>Burning:/Stinging: as reported by the subject within the last 24 hours</i>		
0	None	No burning/stinging
1	Mild	Slight burning sensation; not really bothersome
2	Moderate	Definite warm, burning that is somewhat bothersome
3	Severe	Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep
<i>All of the below will be assessed by the investigator as present or absent.</i>		
<i>Skin Atrophy:</i>		
No	Skin atrophy not present	
Yes	Skin atrophy present	
<i>Striae:</i>		
No	Striae not present	
Yes	Striae present	
<i>Telangiectasias:</i>		
No	Telangiectasias not present	
Yes	Telangiectasias present	
<i>Folliculitis:</i>		
No	Folliculitis not present	
Yes	Folliculitis present	

**11.3.2 Medical History and Abbreviated Physical Examination**

A medical history will be taken at Screening, and confirmed and revised if needed, at Baseline. Medical histories having resolved 2 or more years before Baseline need not be collected unless considered relevant by the investigator.

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An abbreviated physical examination including measurements of weight and vital signs (blood pressure, heart rate, respiration rate, and oral temperature) will be performed at Baseline, Week 8, and Week 12 (post-treatment follow-up visit). Height will be measured at Baseline only. Any abnormal physical exam findings will be recorded.

### **11.3.3 Safety Laboratory Tests**

Routine safety laboratory tests (CBC/Diff and serum chemistry) will be performed at Screening, Week 4, and Week 8. Any out-of-range laboratory result that is considered clinically significant by the investigator will be recorded as an AE and should be confirmed by repeat testing at the discretion of the investigator. Clinically significant laboratory abnormalities at any visit will be followed to resolution (return to normal or to the baseline state) or until clinically stable as determined by the investigator.

### **11.3.4 Pregnancy Tests**

All female subjects of childbearing potential will undergo serum pregnancy testing at Screening, Week 4, and Week 8. In addition, urine pregnancy testing will be performed at Screening and prior to randomization at Baseline, and at Week 12 (4-week post-treatment follow-up visit).

## **11.4 Other Evaluations**

### **11.4.1 Dermatology Life Quality Index (DLQI)**

The DLQI questionnaire will be administered to subjects at Day 0 (Baseline), Week 4, Week 8/End of Treatment and Week 12 (4-week post-treatment follow-up visit).

### **11.4.2 Photography**

Photographs will be taken of target lesion and one other psoriasis lesion at all study visits starting with baseline. Only subjects who provide written photographic consent will be included in photography. Reference the photography manual for this study.

## **11.5 Adverse Events**

### **11.5.1 Definition of Adverse Event**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the study drug. AEs include any unfavorable and unintended illness, sign, symptom, clinically significant laboratory test abnormality, or disease temporally associated with the use of a medicinal product that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the study drug(s) under study. The collection of nonserious AEs and serious adverse events (SAEs) should begin following the subject's completion of the consent process to participate in the study.

### 11.5.2 Documenting Adverse Experiences

It is the responsibility of the investigator to document all AEs that occur during the course of the study. The AEs should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject at each study visit.

All AEs occurring after the subject signs the informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered drug-related. All AEs, whether in response to a query, observed by the study site personnel, or reported spontaneously by the subject, will be recorded.

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Cutaneous tolerability signs and symptoms that result in the subject's requiring a concomitant therapy or discontinuation from the study will be reported as an AE. The following data will be collected on all AEs and recorded on the appropriate eCRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms)
- Onset date and end date
- Maximum intensity (severity)
- Seriousness
- Action taken regarding study drug
- Corrective treatment, if given
- Outcome

In addition, the investigator's assessment of causality will be recorded.

Vital sign abnormalities are to be recorded as AEs only if they are clinically significant (for example: are symptomatic, requiring corrective treatment, leading to discontinuation or fulfilling a seriousness criterion).

### 11.5.3 Serious Adverse Events

All AEs will be assessed as either serious or nonserious.

An SAE or serious adverse reaction is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life threatening, (the term "life threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in patient hospitalization or prolongation of existing hospitalization (hospitalization for elective surgery for a baseline condition is not considered an AE)
- Results in persistent or significant disability/incapacity (permanent or substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the above listed outcomes

Note: A spontaneous abortion will be considered an SAE, and must be reported to the sponsor/designee within 24 hours of your awareness of the event.

### 11.5.4 Assessment of Severity

The severity assigned to an AE should be determined by the maximum severity of the AE. The categories described below should be used to estimate the severity of AEs:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required
- Severe: Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible; may be incapacitating or life threatening

### 11.5.5 Assessment of Causality

The investigator should assess the relationship of the AE, if any, to the study drug as either “Related” or “Not Related”. The following should be taken into account when assessing SAE causality:

- Positive temporal relationship to study drug, such as if the study drug was withdrawn and the SAE resolved or the event recurred after re introduction.
- If there is a reasonable possibility that the AE is associated with an underlying or concomitant illness.
- Possible association with previous or concomitant therapy.
- No temporal relationship to the study drug and/or a more likely alternative etiology exists.
- If the AE is directly related to study procedures or there is a lack of efficacy.

### 11.5.6 Reporting of Serious Adverse Events

Adverse events classified as “serious” require expeditious handling and reporting to sponsor or designee within 24 hours of investigational center notification to comply with regulatory requirements.

All SAEs, whether related or unrelated to study drug, must be immediately reported to the medical monitor within 24 hours of the investigator’s awareness of the event. All SAEs must be reported via confirmed facsimile transmission and must be submitted on a written SAE report form signed by the investigator within 24 hours of the investigator’s awareness of the event.

The fax number for reporting an SAE is:



Investigators should not wait to receive additional information to fully document the event before notifying Medical Monitor of an SAE. If only limited information is initially available, follow-up reports are required. Additional relevant information such as hospital records and autopsy reports should be provided to Sponsor/designee as soon as they are available. Should the investigator become aware of an SAE (regardless of its relationship to investigational product) that occurs within 30 days after stopping the study drug, the SAE must be reported in accordance with procedures specified in this protocol.

The investigator should take all appropriate measures to ensure the safety of the subjects, notably he/she should follow a subject with an SAE until the event has resolved or the condition has stabilized. This may imply that follow-up will continue after the subject has left the study, and that additional investigations may be requested by the sponsor.

#### **11.5.7 Expedited Serious Adverse Event Reports**

An AE, whether serious or nonserious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator Brochure or if the event is of greater frequency, specificity or severity.

Expedited SAE reports are those that are both unexpected based on the reference document (Investigator Brochure or Package Insert) and are related (i.e., the relationship cannot be ruled out) to the study drug. These expedited reports are subject to reporting timelines of 7 and/or 15 calendar days to the regulatory reporting agency(ies). Valeant Pharmaceuticals will notify regulatory authorities of these AEs and all participating investigational centers in writing for submission by the investigator to the IRB/IEC. This notification will be in the form of a Safety Update to the Investigator Brochure (i.e., “15-day letter”).

Upon receiving such notices, the investigator must review and retain the notice with the Investigator Brochure and immediately submit a copy of this information to the responsible IRB/IEC according to local regulations. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

#### **11.5.8 Laboratory Test Abnormalities**

If an AE should require laboratory testing in addition to that required by protocol, the results of the test(s) must be obtained by the investigational center and filed with the subject’s source documentation. Any laboratory test result that meets the criteria for an SAE must also be reported to the sponsor/designee via written SAE report form signed by the investigator within 24 hours of investigational center notification.

#### **11.5.9 Pregnancy**

All female subjects of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of contraceptive failure is minimized. Abstinence is allowed as a birth control method.

Before enrolling a female subject of childbearing potential in this clinical trial, the investigator must review the following information about study participation:

- Informed consent requirements
- Contraceptives in current use

Following review of this information and appropriate subject counseling, the investigator or designee and the subject must sign the informed consent before study enrollment.

During the study, all female subjects of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to study enrollment, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study drug and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the study drug must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the subject will be followed until the pregnancy comes to term. A Pregnancy Report form will be submitted to the sponsor, initially and at the end of the pregnancy, which includes the outcome of the pregnancy and any complications occurring during the pregnancy or the delivery.

All confirmed pregnancies must be immediately reported to the medical monitor within 24 hours of the investigator's awareness of the pregnancy. All confirmed pregnancies must be reported via confirmed facsimile transmission and must be submitted on a written Pregnancy Report form within 24 hours of the investigator's awareness of the pregnancy.

## 12 Statistics

All statistical processing will be performed using SAS<sup>®</sup> unless otherwise stated. No interim analyses are planned. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation, median, minimum, and maximum. Appropriate inferential statistics will be used for the primary and secondary efficacy variables.

The primary method of handling missing efficacy data will be the method of Markov Chain Monte Carlo (MCMC) multiple imputation. As a sensitivity analysis, the last observation carried forward method (LOCF) will be used (i.e., the last available on-therapy observation for a subject will be used to estimate subsequent missing data points). No imputations will be made for missing safety data.

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

## **12.1 Assessment of Efficacy**

The primary efficacy endpoint will be the percent of subjects with treatment success, defined as at least a 2-grade improvement from Baseline in IGA score and an IGA score equating to “Clear” or “Almost Clear”.

### **12.1.1 Primary Efficacy**

The primary efficacy endpoint will be used to compare once daily application of IDP-122 Lotion and vehicle.

The percent of subjects with treatment success at Week 8 will be analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by analysis center.

### **12.1.2 Secondary Efficacy**

Similar to the primary endpoint analyses comparisons will be performed using CMH tests stratified by analysis center. The secondary efficacy endpoints will be:

- Percentage of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at Week 12 for IDP-122 Lotion verses IDP-122 Vehicle Lotion
- Percentage of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at Week 6 for IDP-122 Lotion verses IDP-122 Vehicle Lotion
- Percentage of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at Week 4 for IDP-122 Lotion verses IDP-122 Vehicle Lotion
- Percentage of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at Week 2 for IDP-122 Lotion verses IDP-122 Vehicle Lotion

Evaluation of the secondary efficacy variables will use a gated sequential procedure starting with the comparisons of the first bulleted item and proceeding onto the next item. The process will terminate if a nonstatistically significant value is observed.



### 12.1.3 Tertiary Efficacy

The follow tertiary efficacy endpoints will be analyzed to further characterize the treatment effect of IDP-122 Lotion over the IDP-122 Vehicle Lotion. The analyses will use CMH testing stratified by analysis center without adjusting for multiplicity.

- Percentage of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Week 8 for the target lesion
- Percentage of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Week 12 for the target lesion
- Percentage of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Week 6 for the target lesion
- Percentage of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Week 4 for the target lesion
- Percentage of subjects with at least a 2-grade improvement from Baseline in the score for each of the signs of psoriasis (erythema, plaque elevation, and scaling) at Week 2 for the target lesion

### 12.1.4 Pooling Analysis

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each study site. The study is intended to be conducted in a manner such that a minimum of 15 subjects will be randomized and included in the ITT population (i.e., approximately at least 10 subjects in the IDP-122 arm and at least 5 subjects in the Vehicle arm) for any investigator. In the event that there are too few subjects in a treatment arm for an investigator, then the investigator's data will be combined to achieve the desired sample size minimum per treatment arm. The combining of investigator data will be accomplished by taking the investigator with the smallest enrollment and combining it with the investigator with the largest, restricted to investigational sites that did not meet minimum enrollment. If there is a further need to combine data, then the data of the investigator with the second smallest enrollment will be combined with the investigator's data which had the second largest enrollment, and so on. This process will continue for all investigators who did not have a minimum of 15 subjects enrolled. The process of combining investigator data that have insufficient subjects per treatment arm will result in redefining the groups of investigators for the purposes of statistical analyses. These combined groups will be referred to as "analysis centers" in the statistical analyses.

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The consistency of treatment response will be investigated across the analysis centers subsequent to combining the data as described above. Statistical tests will be conducted to identify if there are extreme analysis centers that could affect the interpretation of common statistical and clinical conclusions. For the purpose of testing consistency of treatment response, the primary efficacy variable will be considered. The percent of subjects with treatment success at Week 8 will be analyzed with a logistic regression with factors of treatment group, analysis center, and the interaction term of treatment group by analysis center. Further examination will follow if the analysis results in a significant interaction term.

In the event that the logistic regression interaction p-value is less than or equal to 0.10, a sensitivity analysis that excludes analysis centers with the extreme efficacy result will be performed to determine the robustness of the treatment effect. On the other hand, if the analysis results in an interaction terms with p-value greater than 0.10, then the conclusions from the pooled data will be considered to be free of the impact of extreme analysis centers.

The first step in conducting a sensitivity analysis is to identify the extreme analysis center or centers that contribute to the statistical significance of the interaction term of the logistic regression. The process involves submitting subsets of analysis centers to the logistic regression and observing the interaction p-value for the subset. Subsets resulting in interaction p-values greater than 0.10 are considered homogeneous.

The search for an extreme analysis center begins by analyzing all subsets that can be created by excluding 1 analysis center. If 1 or more of the subsets result in an interaction p-value greater than or equal to 0.10, then the analysis center excluded from the subset with the largest interaction p-value is deemed the extreme analysis center.

If all subset interaction p-values are less than or equal to 0.10, then the process will analyze the interaction for all subsets that can be created by excluding 2 analysis centers. If 1 or more of these subsets generate interaction p-values larger than 0.10, then the analysis centers excluded from the subset with the largest interaction p-value are deemed the extreme analysis centers.

Thus, the process of identifying the extreme analysis centers will continue in a stepwise manner by first excluding 1, then 2, then 3, etc, analysis centers until the logistic regression interaction p-value exceeds 0.10.

Once the extreme analysis center or centers have been identified, then the treatment p-values of the remaining analysis centers will be computed. Inferences will be drawn from the treatment p-value, as well as any pertinent observations regarding the extreme analysis center or centers. Additionally, it is noted that this process excludes subjects from the analysis in a nonrandom manner and has an unpredictable impact on the power of the treatment effect test.

In the event that the treatment effect of the remaining subset is not statistically significant, due consideration of the post hoc aspects of the process will be given when the results are interpreted. Conclusions will be presented by the sponsor as appropriate to the findings of the sensitivity analysis.

Prior to investigating the treatment effect within the analysis centers, the magnitude of the site main effect will be investigated to determine if the main site-to-site variability is such that it could mask the analysis center effects. Thus, prior to pooling, the percent of subjects with treatment success at Week 8 will be analyzed with a logistic regression with factors of treatment group, site, and the interaction term of treatment group by site. If the analysis is not computationally feasible due to some sites having very few subjects enrolled, the low-enrolling sites will be excluded from the analysis.

### **12.1.5 Missing Efficacy Data Imputations**

The primary method of handling missing efficacy data will be MCMC multiple imputation. This method does not rely on the assumption of data missing at random. Additionally, imputation will be conducted within each treatment group independently, so the pattern of missing observations in 1 treatment group cannot influence missing value estimations in another.

For each efficacy variable (IGA and psoriasis signs), the following steps will be performed to impute missing data:

1. Calculate the number of missing Week 8 values to be estimated by MCMC in each treatment group. Let  $n_{miss}$  be the maximum number of missing Week 8 values among the treatment groups.
2. For each treatment group, create a data set containing subjects with observed values and those needing estimation by MCMC. The missing efficacy data in each data set will be filled in using the MCMC method '5 x  $n_{miss}$ ' times to generate '5 x  $n_{miss}$ ' data sets. The resulting data set for each treatment group will be combined into 1 complete data set for each imputation. Options will be included in each imputation process to prevent estimating values to be outside the range of expected values for the assessment.
3. Imputed data will be used to determine dichotomized success/failure values.
4. Each complete data set will be analyzed with the appropriate CMH test.
5. CMH statistics will be normalized using the Wilson-Hilferty transformation.
6. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

## **12.1.6 Sensitivity Efficacy Analyses**

### **12.1.6.1 Analyses Using Last Observation Carried Forward**

In the first set of sensitivity analyses, missing IGA values will be imputed using LOCF. Treatment success at Week 8 will be analyzed as it was in the primary analyses. Comparisons will be performed on imputed data using CMH tests stratified by analysis center.

### **12.1.6.2 Repeated Measures Analysis on Observed Data**

As a second sensitivity analysis, treatment success at Week 8 will be analyzed with a repeated measures logistic regression model (generalized estimating equations), with treatment success as the dependent variable and treatment, analysis center and visit (Weeks 2, 4, 6 and 8) as independent factors.

## **12.1.7 Subgroup Analyses**

Subgroup analyses will be conducted for the ITT population for the following subgroups: Baseline IGA, sex, age, ethnicity, and race. Age will be dichotomized to less than the median age of subjects and greater than or equal to the median age of subjects. Subgroup analyses will be conducted on the primary efficacy endpoint and will contain only descriptive statistics.

## **12.2 Assessment of Safety**

### **12.2.1 Adverse Events**

The primary analysis of safety will be conducted at Week 8. There will be a tabulation, however, of the AE's that start in the period post the Week 8 to Week 12 visit. All AEs occurring during the study will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent adverse events (TEAEs), defined as any AE with an onset on or after the date of first study drug application, will be summarized by treatment group and will provide the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to study drug. When summarizing TEAEs by severity or relationship to study drug, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported SAEs will be summarized by the number of subjects reporting the event, system organ class, preferred term, severity, and relationship to study drug.

All information pertaining to AEs noted during the study will be listed by treatment group and subject and will include a verbatim description of the event as reported by the investigator, as well as the preferred term, system organ class, start date, stop date (if stopped), seriousness, severity, action taken regarding the study drug, corrective treatment, outcome, and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided as well as a listing of subjects who reported an SAE.

### **12.2.2 Local Skin Reactions**

The frequency of local skin reactions including itching, dryness, burning/stinging, skin atrophy, striae, telangiectasia and folliculitis will be summarized by treatment group and visit. Additionally, the percent of subjects who experience a local skin reaction (itching, dryness, burning/stinging) graded at a level of 3, at any point in the study following the first application of study drug, will be tabulated by treatment group.

### **12.2.3 Safety Laboratory Values and Vital Sign Measurements**

Changes from Baseline in safety laboratory values and vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits.

Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at Baseline and Weeks 4 and 8. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment time point will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

### **12.3 Subject Disposition**

A tabulation of subject disposition will be provided. The tabulation will include the numbers of subjects who enter the study, complete the study, and discontinue the study. The reasons for discontinuation will be included.

### **12.4 Demographics and Baseline Characteristics**

Subject demographic data and Baseline characteristics will be summarized by treatment group using descriptive statistics for the ITT, PP, and safety analysis sets. Comparisons between treatment groups will be performed to ensure comparable results.

### **12.5 Protocol Deviations**

All protocol deviations will be reported to the sponsor and recorded throughout the study. A tabulation of protocol deviations will be included in the final study report.

## 12.6 Compliance

No formal evaluations of compliance are planned.

## 12.7 Interim Analyses

No interim analyses are planned.

## 12.8 Additional Statistical Considerations

### 12.8.1 Analysis Populations

Approximately 210 adult subjects with moderate or severe psoriasis (defined as an IGA score of 3 or 4) will be enrolled and randomized in the study. With a 2:1 randomization ratio, it is anticipated that:

- Approximately 140 subjects will be randomized to receive IDP-122 (HP 0.01%) Lotion
- Approximately 70 subjects will be randomized to receive IDP-122 Vehicle Lotion

Efficacy analyses will be performed using the intent-to-treat (ITT) population and the per protocol (PP) population. The ITT analysis set will be considered primary for the evaluation of efficacy. Safety analyses will be performed using the safety population.

All subjects who are randomized and dispensed study drug will be included in the ITT analysis set.

All subjects who are randomized, receive at least 1 confirmed dose of study drug and have at least 1 post-baseline safety assessment will be included in the safety analysis set.

All subjects in the ITT analysis set who complete the Week 8 visit without any major protocol violations will be included in the PP analysis set. The PP population will include subjects in the ITT population who did not meet any of the following criteria:

- Violated the inclusion/exclusion criteria
- Used an interfering concomitant medication
- Did not attend the Week 8 visit
- Missed more than 1 post-baseline study visit prior to Week 8
- Have not been compliant with the dosing regimen (i.e., subjects must apply 80%-120% of the expected applications of study medication during participation in the study)
- Out of visit window at the Week 8 visit by more than  $\pm 5$  days

Subjects that discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect will be included in the PP population. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

The number of subjects in each analysis set will be summarized. Reasons for study withdrawal during the blinded study will be summarized using frequencies and percentages by treatment group.

### 12.8.2 Sample Size Determination

The following power calculations were computed using the observed Week 8 dichotomized IGA efficacy data in the ITT population from the Phase 2 study V01-118A-201. SAS PROC POWER with the Fisher's exact test option was used to calculate the power for various sample sizes using a two-sided test with an alpha of 0.05. Table 5 presents the efficacy estimates derived from study V01-118A-201.

**Table 5. Percent Dichotomized IGA Success for Treatment Groups**

	IDP-122* (IDP-118 Monad (HP 0.01%) Lotion)	IDP-122 (IDP-118)** Vehicle
Percent Success	33.3%	9.7%

Success was defined as at least a 2-grade improvement from Baseline in the IGA score and an IGA score equating to "Clear" or "Almost Clear".

\*IDP-122 refers to the (IDP-118 Monad (HP 0.01%) Lotion) used in the V01-118A-201 Study

\*\*IDP 118 Vehicle composition used in the V01-118A-201 is equivalent to the vehicle that will be used in this study (IDP 122 Vehicle Lotion).

One hundred forty (140) IDP-122 treated subjects and seventy (70) vehicle treated subjects will have greater than 95% power to detect a statistically significant outcome for a two-sided test with an alpha level of 0.05.

It was noted that the estimates extracted from the above studies are based on the LOCF method of handling missing values while the proposed Phase 3 analysis will account for missing values using multiple imputations. The power stated above sufficiently exceeds 95% which will compensate for the difference in handling of missing data.

### **12.8.3 Handling of Missing Data**

The method of multiple imputation will be used (see [Section 12.1.4](#)).

### **12.8.4 Multicenter Issues**

The study will be conducted at multiple investigational centers in North America with the intention of pooling the results for analysis.

### **12.8.5 Multiplicity Issues**

Not applicable.

### **12.8.6 Windowing Rules**

The timing of all study visits is relative to Baseline (Day 0). The Week 2 and 4 visits should occur within  $\pm 3$  days of the scheduled times, the Week 8 visit should occur within  $\pm 5$  days of the scheduled time, and Week 12 visits should occur within  $\pm 7$  days of the scheduled times.

## **13 Quality Control and Quality Assurance**

### **13.1 Study Monitoring**

An Investigator Meeting or an initiation visit will be conducted with the principal investigator and study coordinators by sponsor and/or its designee. During this meeting, an extensive review and discussion of the protocol, the role of the study technician, all study procedures, source documents, and eCRFs will be conducted. Evaluation scales will be reviewed extensively and documentation of training will be recorded for training of sponsor-approved evaluators.

The study monitors/clinical research associates will be trained prior to study initiation. Following this training, an overview of the study disease and study material background will be understood. Specific monitoring guidelines and procedures to be followed during monitoring visits will also be utilized. During the course of the study, all data will be 100% source document verified by the monitors. All subject source records must be made available to the monitors.

The conduct of the study will be closely monitored by the sponsor following GCP guidelines. The reports of these verifications will also be archived with the study report. In addition, inspections or on site audits may be carried out by local authorities or by the sponsor's Quality Assurance Department. The investigators will allow the sponsor's representatives and any regulatory agency to examine all study records, corresponding subject medical records, clinical dispensing records and storage area, and any other documents considered source documentation. The investigators agree to assist the representative, if required.



### **13.2 Audits and Inspections**

The study will be conducted under the sponsorship of Valeant in conformation with all appropriate local and federal regulations, as well as ICH guidelines. Interim and end of study audits of raw data, study files, and final report may be conducted by Valeant's Quality Assurance Department or designee.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. In addition, the sponsor will be responsible for securing agreement from all involved parties to ensure direct access to all study related investigational centers, source data/documents, eCRFs, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

### **13.3 Data Quality Assurance**

All assessments performed will be accurately documented in the subject's source documents and eCRFs. The investigator or designee will enter the information required by the protocol into the source documents and eCRFs provided by the sponsor or designee. Subjects will be identified in the eCRFs by their assigned subject number and initials only.

The investigators must read the protocol thoroughly and must follow the instructions exactly. Any deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate written protocol amendments made prior to implementing the agreed changes. Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

## **14 Ethics and Administrative Issues**

### **14.1 Ethical Conduct of the Study**

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP, and in compliance with local regulatory requirements. The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

## **14.2 Ethics Review**

This protocol, proposed informed consent form and other information to subjects, and all appropriate amendments will be properly reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC). A signed and dated notification of the IRB/IEC approval will be provided to the sponsor and investigator prior to study initiation. The name and occupation of the chairman and members of the IRB/IEC will be supplied to the sponsor. The investigator will provide required progress reports and report all SAEs to the IRB/IEC as required by the IRB/IEC.

## **14.3 Written Informed Consent**

Written informed consent, in accordance with local clinical investigation regulations, must be obtained prior to participation in the study. The investigator or designee will discuss the purpose of the study with each subject, and provide a description of the study drug (including any potential and possible side effects) and the study procedures. Information must be given both in oral and written form. Subject information will be provided in a language understandable to the subject and may not include any language that appears to waive any of the subject's legal rights or appears to release the investigator, the sponsor or the institution from liability or negligence.

The investigator will provide the prospective subject sufficient time to consider whether or not to participate, minimizing the possibility of coercion or undue influence and will discuss any questions the subject may have. The investigator will explain to the subject that participation in the study is voluntary and that withdrawal from the study is possible at any time without detriment to care. The consent must include acknowledgment that medical records and medical data derived from the study may be forwarded to the sponsor or to responsible local or federal authorities.

No subject can enter the study or have any study related procedures performed before his/her written informed consent has been obtained. The original signed and dated informed consent form will be retained with the study records, and a copy of the signed form will be given to the subject.

An informed consent template will be supplied by the sponsor. Any changes to the informed consent form must be agreed to by the sponsor or designee prior to submission to the IRB/IEC, and a copy of the approved version must be provided to the sponsor or designee after IRB/IEC approval.

#### **14.4 Subject Data Protection**

Subject data will be protected by ensuring that no captured data contain subject names, addresses, telephone numbers, email addresses, or other direct personally identifying information. It is acknowledged that subject initials, demographics (including birthdates), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study participants. Other than where necessary to meet regulatory requirements, all data collected in this study will be presented in tabulated (i.e., aggregate) form and listings containing information that could be used to identify an individual subject will not be included in any public disclosures of the study data or the study results.

#### **14.5 Data Monitoring Committee**

Not applicable.

#### **14.6 Financial Disclosure**

Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest.

#### **14.7 Investigator Obligations**

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice (GCP).

#### **14.8 Changes to the Protocol**

The investigators must read the protocol thoroughly and must follow the instructions exactly. Whenever possible, any planned deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate documentation of sponsor approval prior to effecting the changes agreed upon. Any amendment to the protocol containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

#### **14.9 Confidentiality/Publication of the Study**

All the data furnished to the investigator and his/her staff and all data obtained through this protocol will be regarded as confidential and proprietary in nature and will not be disclosed to any third party, except for the FDA or other regulatory body, without written consent from the sponsor.

## 15 Data Handling and Record Keeping

### 15.1 Inspection of Records

Investigators must maintain detailed records on all study subjects who are enrolled in the study or undergo screening. Data will be recorded in the subject's source documents and in applicable study logs provided by the sponsor. Source documents include subject medical records, hospital charts, clinic charts, investigator subject study files, as well as the results of diagnostic tests (e.g., laboratory tests). All required data should be recorded in the study documentation completely for prompt data review. Upon study completion or at any other time specified by the sponsor or designee, the appropriate study documents must be submitted.

The investigator must keep accurate separate records (source documentation) of all subject visits, being sure to include all pertinent study related information. At a minimum, this includes the following information:

- A statement indicating that the subject has been enrolled in the study and the subject number
- Date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (e.g., medical history, screening evaluations)
- Dates of all study related visits and results of any evaluations/procedures performed, including who performed each assessment at each visit
- Use of any concurrent medications during the study
- Documentation of study drug accountability
- Any and all side effects and AEs must be thoroughly documented to conclusion
- Results of any diagnostic tests conducted during the study
- The date the subject exited the study and a statement indicating that the subject completed the study or was discontinued early, including the reason for discontinuation

Notes describing telephone conversations and all electronic mail with the subject or the sponsor (sponsor's designee) concerning the study must be recorded or kept on file. All source documents must be made available to the sponsor and the sponsor's designated monitor upon request.

## **15.2 Retention of Records**

The investigator should properly store and maintain all study records in accordance with sponsor directives. All records relating to the conduct of this study are to be retained by the investigator until notified by the sponsor in writing that the records may be destroyed.

The investigator will allow representatives of the sponsor's monitoring team, the governing IRB/IEC, the FDA, and other applicable regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's clinic and/or hospital medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness and accuracy of the data being entered onto the eCRF, and compliance with FDA or other regulatory agency regulations.

## **16 References**

Not applicable.

## 17 Appendices

### 17.1 Subject Instruction Sheet

A thin layer of study drug should be applied **once daily** at about the same time each day over the affected treatment areas indicated by the investigator for 8 weeks. As a reminder, the face, scalp, axillae (armpit) and intertriginous (skinfold) areas will be excluded.

Specifically, subjects will squeeze a small amount of study drug (about the size of a pea) onto a fingertip and then spread a thin layer of the study drug over the affected treatment area. If necessary, additional pea-sized amounts of study drug may be applied in increments (one pea size gently rubbed over a treatment area at a time) to cover all affected treatment areas.

The amount of study drug used by the subjects will be monitored by weighing each newly dispensed study drug container and weighing each returned study drug container at all applicable study visits. The maximum allowable weekly usage is 50 grams for this study.

Be sure to wash your hands after you apply the product (unless the study doctor has instructed you to treat your palms).

Reminders:

- On study visit days please wait until after your study assessments are completed before application of the study drug or any approved moisturizers. Any retraining can be provided by site staff, if needed.
- Avoid contact with the eyes, inside the nose, mouth and all mucous membranes.
- THE TEST MATERIAL SHOULD BE USED ONLY BY THE PERSON FOR WHOM IT WAS PRESCRIBED and it should be kept out of the reach of children or others of limited capacity to read or understand.

Store this at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F).

Containers of test material must be returned to the study facility, even if they are empty.

Be sure to complete the diary calendar each day to document applications and also note any missed doses; and bring the completed diary to each study visit.

Continue to use the same study doctor approved non-medicated cleansers, moisturizers and sunscreens throughout the study. Avoid or minimize unnecessary sun exposure. Also for further ultraviolet protection use protective clothing such as broad brimmed hats as needed.

It is important that you inform the study site about any medications (i.e., prescriptions, over-the-counter medications, street drugs, or herbal medications) that you have taken during the study.

If you have any questions or have a potential research-related side effect or injury you may contact \_\_\_\_\_ at \_\_\_\_\_.

## 17.2 Cleanser, Moisturizer and Sunscreen Use Guidelines

Investigators may use their discretion on what cleansers and moisturizer products each subject may use in the treatment areas during the study. Subjects may only use Investigator approved non-medicated products on the treatment areas. Information regarding products used should be captured in the source document and recorded on the Prior and Concomitant Medications or Therapies eCRF.

### Approved Cleanser Examples:

- CeraVe cleanser
- Cetaphil daily cleaner and gentle cleansing bar
- Purpose gentle cleansing wash
- Investigator-approved non-medicated cleanser

### Approved Moisturizer Examples:

- CeraVe Cream or Lotion
- Moisturel cream or lotion
- Nutraderm
- Cetaphil lotion or cream
- DML
- Eucerin lotion or cream
- Purpose

Subjects should avoid excessive sun exposure, but when this can't be avoided, an approved sunscreen may be used. Also for further ultraviolet protection use protective clothing, such as broad brimmed hats, as needed.

### Approved Sunscreen Examples:

- Banana Boat Sport Sunblock Lotion (SPF 15, 30+ or 50)
- Neutrogena UVA/UVB (SPF 30 or 45)
- Neutrogena Sensitive Skin Sunblock Lotion (SPF 17)
- Neutrogena Healthy Defense Oil-Free Sunblock Lotion (SPF 30 or 45)
- Coppertone Water Babies UVA/UVB Sunblock Lotion (SPF45)

### 17.3 Dermatology Life Quality Index (DLQI) Questionnaire

**DERMATOLOGY LIFE QUALITY INDEX**

Hospital No:  
Name:  
Address:

Date:  
Diagnosis:

DLQI  
Score:

**The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick  one box for each question.**

- |     |   |  |                                       |
|-----|---|--|---------------------------------------|
| 1.  | Over the last week, how <b>itchy, sore, painful or stinging</b> has your skin been?   | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> |                                       |
| 2.  | Over the last week, how <b>embarrassed</b> or <b>self conscious</b> have you been because of your skin?   | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> |                                       |
| 3.  | Over the last week, how much has your skin interfered with you going <b>shopping</b> or looking after your <b>home or garden</b> ?                  | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 4.  | Over the last week, how much has your skin influenced the <b>clothes</b> you wear?  | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 5.  | Over the last week, how much has your skin affected any <b>social</b> or <b>leisure</b> activities?   | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 6.  | Over the last week, how much has your skin made it difficult for you to do any <b>sport</b> ?   | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 7.  | Over the last week, has your skin prevented you from <b>working</b> or <b>studying</b> ?  | Yes <input type="checkbox"/><br>No <input type="checkbox"/>  | Not relevant <input type="checkbox"/> |
|     | If "No", over the last week how much has your skin been a problem at <b>work</b> or <b>studying</b> ?   | A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/>                                       |                                       |
| 8.  | Over the last week, how much has your skin created problems with your <b>partner</b> or any of your <b>close friends</b> or <b>relatives</b> ?      | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 9.  | Over the last week, how much has your skin caused any <b>sexual difficulties</b> ?  | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 10. | Over the last week, how much of a problem has the <b>treatment</b> for your skin been, for example by making your home messy, or by taking up time? | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |

**Please check you have answered EVERY question. Thank you.**

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### 17.4 Summary of Protocol Amendment 1 Changes

<i>Section</i>	<i>Original Protocol Previously Read:</i>	<i>Protocol Amendment 1 Currently Reads:</i>
2.0 Study Synopsis Methodology 7.1 Overall Study Design and Plan: Description 17.1 Subject Instruction Sheet	The subjects will be instructed to avoid exposure to direct sunlight to prevent sunburn.	The subjects will be instructed to avoid exposure to direct sunlight, artificial ultraviolet light sources and to use protective clothing to prevent sunburn.
2.0 Study Synopsis Methodology 11.1 Visit Descriptions 7.1 Overall Study Design and Plan: Description 17.1 Subject Instruction Sheet	During the study, subjects will be allowed to use investigator approved non medicated cleansers and moisturizers; no sunscreens or other skin care products will be permitted on the treatment areas.	During the study, subjects will be allowed to use investigator approved non-medicated cleansers, moisturizers and sunscreens; no other skin care products will be permitted on the treatment areas.
2.0 Study Synopsis Methodology Key Exclusion Criteria 8.2 Subject Exclusion Criteria	7. Has used any phototherapy (including laser), photochemotherapy, or systemic psoriasis therapy (such as systemic corticosteroids, methotrexate, retinoids or cyclosporine) within 4 weeks prior to the Baseline visit.	7. Has used any phototherapy (including laser), photochemotherapy, or non-biologic systemic psoriasis therapy (such as newer oral psoriasis medications (eg Otezla), systemic corticosteroids, methotrexate, retinoids or cyclosporine) within 4 weeks prior to the Baseline visit.
2.0 Study Synopsis Methodology Application instructions 9.5 Treatment Compliance 10.1.3 Administration 17.1 Subject Instruction Sheet	N/A	The maximum allowable weekly usage is 50 grams for this study.
2.0 Study Synopsis Methodology Inferential Statistics Secondary Efficacy 12.1.2 Secondary Efficacy	N/A	<ul style="list-style-type: none"> <li>Percentage of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at Week 6 for IDP-122 Lotion versus IDP-122 Vehicle Lotion</li> </ul>
9.4 Prior and Prohibited Concomitant Medication of Therapy	<ul style="list-style-type: none"> <li>Within 4 weeks prior to the Baseline visit, subjects must not have used any phototherapy (including laser), photochemotherapy, or systemic psoriasis therapy (such as systemic corticosteroids, methotrexate, retinoids or cyclosporine)</li> </ul>	<ul style="list-style-type: none"> <li>Within 4 weeks prior to the Baseline visit, subjects must not have used any phototherapy (including laser), photochemotherapy, or non-biologic systemic psoriasis therapy (such as newer oral psoriasis medications (eg Otezla), systemic corticosteroids, methotrexate, retinoids or cyclosporine)</li> </ul>

<i>Section</i>	<i>Original Protocol Previously Read:</i>	<i>Protocol Amendment 1 Currently Reads:</i>
9.4 Prior and Prohibited Concomitant Medication of Therapy	Subjects are allowed only the use of investigator approved non-medicated cleansers and moisturizers in the treatment areas.	Subjects are allowed only the use of investigator approved non-medicated cleansers, moisturizers and sunscreens in the treatment areas.
10.1.1 Packaging and Labeling	IDP-122 Lotion will be packaged in study drug kits.	IDP-122 Lotion and IDP 122 Vehicle Lotion will be packaged in identical study drug kits.
17.1 Subject Instruction Sheet 17.2 Cleansers, moisturizers and sunscreen Use Guidelines		Also for further ultraviolet protection, use protective clothing and broad brimmed hats as needed.
9.5 Treatment Compliance	The subjects will bring the containers dispensed at each on treatment visit to the next subsequent study visit.	The subjects will bring the containers dispensed at each on-site treatment visit to the next subsequent study visit.