DURECT

Official Title:	A Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Proof of Concept Comparison Study of the Safety and Efficacy of DUR-928 Topical Solution With Occlusion in Subjects With Mild to Moderate Plaque Psoriasis
NCT Number:	NCT03837743
Document Date:	May 22, 2019

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PROOF OF CONCEPT COMPARISON STUDY OF THE SAFETY AND EFFICACY OF DUR-928 TOPICAL SOLUTION WITH OCCLUSION IN SUBJECTS WITH MILD TO MODERATE PLAQUE PSORIASIS

PROTOCOL NUMBER:	C928-015
PPD	
IND NUMBER	140,088
ORIGINAL PROTOCOL:	October 29, 2018
PROTOCOL AMENDMENT #1	January 9, 2019
PROTOCOL AMENDMENT #2	February 8, 2019
PROTOCOL AMENDMENT #3	May 22, 2019
FILENAME:	C928-015_protocol_22May2019_v4.0
SPONSOR:	Therapeutics, Inc. 9025 Balboa Avenue, Suite 100 San Diego, CA 92123
SPONSOR REPRESENTATIVE:	PPD
MEDICAL MONITOR:	PPD
PROJECT MANAGER:	PPD

24 Hour Emergency Telephone Number
PPD

Therapeutics, Incorporated
9025 Balboa Avenue, Suite 100, San Diego, CA 92123

PROTOCOL APPROVAL

The following individuals approve version 4.0 of the C928-015 protocol dated May 22, 2019. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

PPD

Date: 24-May 2019

Date: 24-May-2019

Date: 24/May 2019

Date: 24 MAY 2019

STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to PPD

I have read this protocol, agree that it contains all the details necessary to conduct the study as described, and will conduct this study following this protocol.

I will provide the contents of this protocol to study staff under my direct supervision that need to know the contents to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the test articles. I will provide the contents of the protocol to the responsible Institutional Review Board(s). These disclosures may be made; providing the contents are not used in any other clinical study and they are not disclosed to any other person or entity without prior written consent from PPD This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to PPD of any such disclosure.

I understand the study may be terminated or enrollment suspended at any time by PPD with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

Any additional information added to this protocol is also confidential and proprietary to PPD and must be treated in the same manner as the contents of this protocol.

_____
Printed Name of Principal Investigator

_____ _____
Investigator Signature Date

Protocol number: C928-015 Site number: _____

PROTOCOL SYNOPSIS

Title	A Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Proof of Concept Comparison Study of the Safety and Efficacy of DUR-928 Topical Solution with Occlusion in Subjects with Mild to Moderate Plaque Psoriasis
Study Type	Phase 2
Test Articles	1. DUR-928 Topical Solution, C (DUR-928) 2. Vehicle Topical Solution (VEH)
Study Objective	To determine and compare the safety, tolerability, and efficacy of DUR-928 with that of the vehicle control in subjects with plaque psoriasis with occlusion.
Study Design	Multicenter, randomized, double-blind, vehicle-controlled, paired-plaque comparison study.
Treatment Groups	After enrollment in the study, each subject will receive DUR-928 topical solution and vehicle with occlusion for approximately two hours post application. DUR-928 solution will be randomly assigned to one target lesion and vehicle will be assigned to the contralateral target lesion. The assigned test articles will be applied once daily for four weeks.
Duration of Treatment	Once daily application for four weeks.
Duration of Study	Approximately eight weeks for an individual subject.
Study Population	Male or female subjects 18 years of age or older with stable mild to moderate plaque psoriasis.
Total Number of Subjects	Approximately 20 subjects will be enrolled to obtain about 15 evaluable subjects in the study.
Number of Sites	Approximately three sites will participate in the study.
Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Subject is a male or non-pregnant female 18 years of age or older. 2. Subject has provided written informed consent. 3. Subject has a clinical diagnosis of stable mild to moderate plaque psoriasis for at least two months.

	4. Females must be post-menopausal[1], surgically sterile[2], or use an effective method of birth control.[3,4] Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)[5] at Visit 2/Baseline. 5. Males (or their female partner) must agree to use an effective method of birth control throughout the study. 6. Subject has two similar contralateral Target Plaques that: • Are located on the upper extremities not including the palms, and • Must individually be a minimum of 6 cm^2 in area, a maximum of 64 cm^2 in area, and a similar size (both Target Plaques should ideally be the same size but one should not be more than about a third larger [e.g., 33%] than the smaller plaque), and • Must have the same Investigator's Global Assessment (IGA) score of 2 or 3, and • Must have the same plaque elevation score of 2 or 3, and • Have a Target Plaque Comparison score of 0 (Target Plaque A=Target Plaque B), and • Are easily accessible for test article application by the subject or a reliable care provider. 7. Subject is willing and able to apply the test article(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study. 8. Subject, in the investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of the plaque psoriasis or exposes the subject to an unacceptable risk by study participation.
Exclusion Criteria	A subject is ineligible to enter the study if he/she meets one or more of the following criteria: 1. Subject is pregnant, lactating, or is planning to become pregnant during the study.

[1] Defined as amenorrhea greater than 12 consecutive months in women 50 years of age and older.
[2] Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment), or bilateral oophorectomy.
[3] Effective forms of birth control include a) hormonal contraceptives [e.g., oral, transdermal, injectable, implantable, or vaginal ring] (see next footnote), b) intrauterine device (IUD) for at least one week prior to test article application, c) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], d) monogamous relationship with a partner who is sterile [e.g., vasectomy performed at least six months prior to study entry], or e) total abstinence for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.
[4] WOCBP taking hormonal therapy must be on treatment prior to study entry, continued per label, and must not change their dosing regimen during the study; treatment must be for (1) oral: at least one complete cycle (e.g., four to eight weeks); (2) transdermal, injectable (e.g., Depo-Provera), implantable, or vaginal ring (e.g., NuvaRing): at least one week.
[5] UPT must have a minimum sensitivity of 25 mIU ß-hCG/mL.

	2. Subject has spontaneously improving or rapidly deteriorating plaque psoriasis. 3. Subject has guttate, pustular, erythrodermic, inverse, or other non-plaque forms of psoriasis. 4. Subject has any skin pathology or condition that, in the investigator's opinion, could interfere with the evaluation of the test article or requires use of interfering topical, systemic, or surgical therapy. 5. Subject has psoriasis beyond the two Target Plaques that, in the investigator's opinion, could not be reasonably managed with only bland emollient, triamcinolone cream, 0.1%, or over the counter (OTC) hydrocortisone during the study. 6. Subject has used any systemic methotrexate, retinoids, systemic corticosteroids (including intralesional, intra-articular, and intramuscular corticosteroids), cyclosporine, tofacitinib, apremilast, or analogous products within 90 days prior to Visit 2/Baseline. 7. Subject has used any systemic immunomodulatory biologic therapy (i.e., FDA-approved or experimental therapy) within five half-lives of the biologic prior to Visit 2/Baseline. Published or documented half-life of the product provided by the commercial supplier or Sponsor should be used to establish this value. 8. Subject has used any phototherapy (including laser), photo-chemotherapy, or other forms of photo-based therapy for the treatment of their psoriasis within 30 days prior to Visit 2/Baseline. 9. Subject had prolonged exposure to natural or artificial sources of ultraviolet radiation within 30 days prior to Visit 2/Baseline or is intending to have such exposure during the study which, in the opinion of the investigator, is thought to modify the subject's disease. 10. Subject has used topical body (excluding the scalp) psoriasis therapy (including coal tar, anthralin, steroids, retinoids, and vitamin D analogs) within 14 days prior to Visit 2/Baseline. 11. Subject has undergone treatment with Vitamin A supplements within 14 days prior to Visit 2/Baseline. 12. Subject has used emollients/moisturizers on areas to be treated within four hours prior to clinical evaluation at Visit 2/Baseline. 13. Subject is currently using lithium or Plaquenil (hydroxychloroquine). 14. Subject is currently using a beta-blocking medication (e.g., propranolol) or angiotensin converting enzyme (ACE) inhibitor at a dose that has not been stabilized (i.e., on the same dosage for at least four weeks). 15. Subject has a history of cancer, with the exception of successfully treated non-metastatic basal cell and squamous cell carcinoma. 16. Subject is currently enrolled in an investigational drug or device study. 17. Subject has used an investigational drug or investigational device treatment within 30 days prior to Visit 2/Baseline. 18. Subject has been previously enrolled in this study and treated with test article. 19. Subject has a history of sensitivity to any of the ingredients in the test articles. 20. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.

Study Procedures	The study will consist of nine clinic visits. Visit 1 (Day-30 to -1): Screening. Subjects can be screened for the study up to 30 days before Visit 2/Baseline. During Visit 1/Screening, the study requirements will be reviewed and written informed consent must be obtained prior to the initiation of any study-related procedures. Demographics, inclusions/exclusion criteria, medical history, and concomitant medications and procedures/therapies will be reviewed to determine eligibility. A brief physical examination and vital signs will be performed. Height and weight will also be measured. Blood and urine samples will be taken for clinical laboratory tests (chemistry, hematology, and urinalysis) and a UPT (if applicable). Identification and clinical evaluations of Target Plaques (IGA, Target Plaque Area, Clinical Signs and Symptoms including Local Psoriasis Severity Index [LPSI], and Target Plaque Comparison) will be performed. If applicable, the washout from prohibited medications or treatments will be determined and implemented. The subject will be scheduled for Visit 2/Baseline. Visit 2 (Day 1): Baseline. The subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and procedures/therapies. Vital signs and UPT (if applicable) will be performed. Identification of two Target Plaques will be re-confirmed and clinical evaluations of Target Plaques (IGA, Target Plaque Area, Clinical Signs and Symptoms including LPSI, and Target Plaque Comparison) will be performed. Numeric Rating Scale (NRS) for Pruritus will be assessed by the subject prior to test article application. Photography will be performed. Local skin reactions (LSRs) will be assessed prior to test article application. The subject will be randomized by assigning the next available (lowest) test article kit number in ascending order. A Subject Diary and Subject Instruction Sheet will be dispensed. Subjects will be instructed on how to apply the test articles, perform occlusion, take a photograph once daily until the next clinic visit, and to record applications in the Subject Diary. Test article accountability will be documented. The first doses and occlusion will be applied at the site under supervision of study staff. LSRs will be assessed 15 minutes following test article application. Adverse events (AEs) will be recorded. The subject will be scheduled for Visit 3. Visit 3 (Day 8 ± 1): Week 1, Visit 4 (Day 15 ± 2): Week 2, and Visit 5 (Day 22 ± 2): Week 3. The subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and procedures/therapies. Photography and clinical evaluations of Target Plaques (IGA, Clinical Signs and Symptoms including LPSI, and Target Plaque Comparison) will be performed. **Visit 4 only: NRS for Pruritus will be assessed by the subject and Target Plaque Area by the site staff.** LSRs will be assessed. A new Subject Instruction Sheet will be dispensed, if necessary. **It is also important to review proper use of the "correct" test article for each of the two Target Plaques – emphasizing the importance to use the same labeled test article on the same Target Plaque for the duration of the study.** Subject Diary will be collected, reviewed, and dispensed. Test article accountability will be documented. The site staff will remind the subject to continue to apply the test articles, perform occlusion, take a photograph once daily until the next clinic visit, and to

	record all applications in the Subject Diary. AEs will be recorded. The subject will be scheduled for the next visit, as appropriate. Visit 6 (Day 29 + 3): Week 4/End of Treatment (EOT). The subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and procedures/therapies. A brief physical examination and vital signs will be performed. Blood and urine samples will be taken for clinical laboratory tests (chemistry, hematology, and urinalysis) and a UPT (if applicable). Photography and clinical evaluations of Target Plaques (IGA, Target Plaque Area, Clinical Signs and Symptoms including LPSI, and Target Plaque Comparison) will be performed. NRS for Pruritus will be assessed by the subject. LSRs will be assessed. Test article accountability will be documented and all test articles will be collected. Subject Diary will be collected and reviewed. AEs will be recorded. The subject will be scheduled for Visit 7. Visit 7 (Day 36 ± 3): Follow-up 1 and Visit 8 (Day 50 ± 3): Follow-up 2. The subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and procedures/therapies. A directed physical examination, vital signs, and/or clinical laboratory tests will be performed if any of the results from the preceding visit are materially abnormal and clinically significant. Photography and clinical evaluations of Target Plaques (IGA, Clinical Signs and Symptoms including LPSI, and Target Plaque Comparison) will be performed. LSRs and AEs will be documented. The subject will be scheduled for the next visit, as appropriate. Visit 9 (Day 57 ± 3): End of Study (EOS). The subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and procedures/therapies. A directed physical examination, vital signs, and/or clinical laboratory tests will be performed if any of the results from the preceding visit are materially abnormal and clinically significant. Photography and clinical evaluations of Target Plaques (IGA, Target Plaque Area, Clinical Signs and Symptoms including LPSI, and Target Plaque Comparison) will be performed. NRS for Pruritus will be assessed by the subject. LSRs and AEs will be documented. The subject will exit the study.
Study Measurements	The following study measurements will be performed according to the Schedule of Events. The IGA, Clinical Signs of Psoriasis including LPSI, and the Target Plaque Area will be assessed individually for the two Target Plaques. Ideally the same evaluator should grade a given subject during the entire study. Efficacy: *Investigator's Global Assessment* The IGA score is a static evaluation of the overall or "average" degree of severity of each of the two Target Plaques by the investigator or designee as the subject appears on the day of the evaluation. This evaluation takes into consideration the three individual characteristics of psoriasis (plaque elevation, scaling, and erythema) with the IGA score at each visit representing the average of plaque elevation, scaling, or erythema that is

present amongst the two Target Plaques. IGA will be assessed individually for the two Target Plaques on a 5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe.

CLEAR (0)
Scaling: no evidence of scaling
Erythema: no evidence of erythema (except possible residual discoloration)
Plaque Elevation: no evidence of plaque elevation above normal skin level

ALMOST CLEAR (1)
Scaling: limited amount of very fine scale
Erythema: light pink color dominates over all or part of the plaque
Plaque Elevation: very slight elevation above normal skin level, easier felt than seen

MILD (2)
Scaling: mainly fine scales; plaque is partially covered
Erythema: light red to pink dominates over all or part of the plaque
Plaque Elevation: slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped over most of the plaque

MODERATE (3)
Scaling: somewhat coarser scales; a significant portion or all of the plaque is covered
Erythema: red dominates over all or part of the plaque
Plaque Elevation: moderate elevation with rounded or sloped edges on most of the edges of the plaque

SEVERE (4)
Scaling: coarse, thick scales; virtually all of the plaque is covered; rough surface
Erythema: virtually all of the plaque is bright to dusky red
Plaque Elevation: marked to very marked elevation, with hard to very hard sharp edges on virtually all edges of the plaque

Clinical Signs of Psoriasis and Local Psoriasis Severity Index
Plaque elevation (induration), scaling, and erythema will each be scored on a 5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. These evaluations are an assessment of the overall or "average" degree of each of three key characteristics present within each of the two Target Plaques by the investigator or designee as the subject appears on the day of the evaluation and will be assessed individually for each Target Plaque. The LPSI is defined as the sum of scoring for plaque elevation, scaling, and erythema. LPSI will range from 0 to 12, with the highest score representing the more severe disease state.

Target Plaque Area
The surface area of each of the two Target Plaques will be determined by tracing the border of each Target Plaque on a transparency containing a 1 cm^2 grid pattern and then totaling the area contained within the border. Each Target Plaque must individually be a minimum of 6 cm^2 and a maximum of 64 cm^2 in area.

Target Plaque Comparison Score
The overall appearance of the two individual Target Plaques will be evaluated as follows: Target Plaque A is better than Target Plaque B, Target Plaque A is the same as Target Plaque B, or Target Plaque A is worse than Target Plaque B. This evaluation will not be a comparison with the condition at a previous visit, but a comparison of the two Target Plaques to determine which one appears better than the other. Note: the two plaques may have identical IGA scores but still be different based upon the comparison score.

Score	Comparison
1A	Target Plaque A is better than Target Plaque B
0	Target Plaque A is the same as Target Plaque B
1B	Target Plaque A is worse than Target Plaque B

Numeric Rating Scale for Pruritus
Pruritus will be assessed using the Itch Numeric Rating Scale (I-NRS), a self-administered Patient Reported Outcome questionnaire. Subjects will indicate itch severity for each target lesion by circling the integer that best describes the worst level of itching due to psoriasis in the past 24 hours on an 11-point scale anchored at 0, representing "no itching" and 10, representing, "worst itch imaginable" The study staff should review the NRS for Pruritus with each subject and ask them to indicate the response that best describes their experience. Pruritus assessed by this evaluation should be reported as an AE only if therapy is required.

Digital Photography
Digital photographic records of the two Target Plaques (A & B) will be generated for each plaque site at each visit (except Visit 1/Screening) before the first application of test article. To help with treatment identification, each Target Plaque site will be marked by a specific label on the photographs

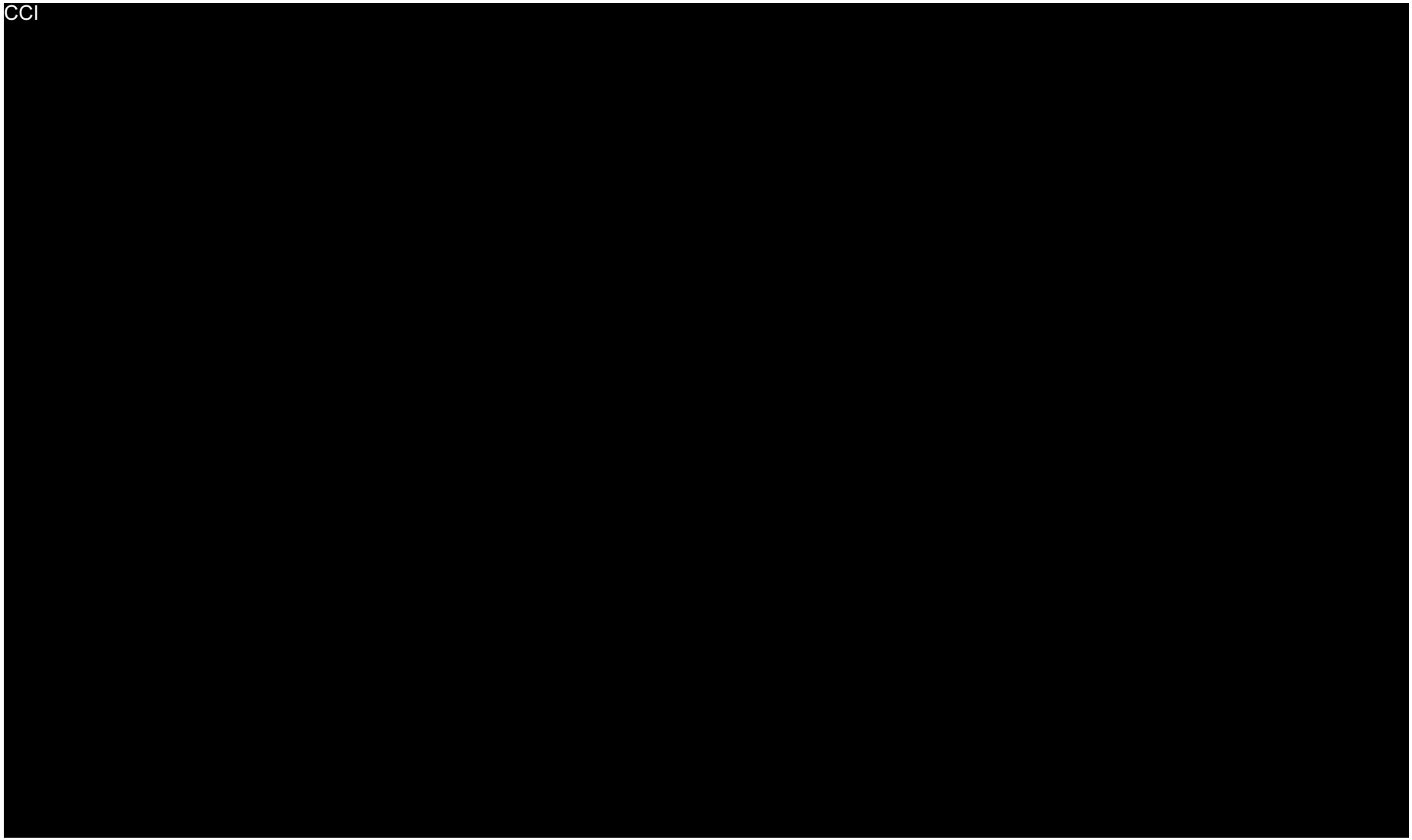
	taken. Photographs of test sites will be taken under identical conditions, as much as possible, to enable proper comparisons to be made as detailed in the Study Photo Guide. Safety: *Adverse Events* All AEs will be recorded. At each visit (except Visit 1/Screening), subjects will also be questioned specifically about the status of any ongoing AEs. *Brief Physical Examination* A brief physical exam will be performed at Visit 1/Screening and Visit 6/EOT. The exam will include examination of head and neck, dermatological, cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait. Abnormalities at Visit 1/Screening will be recorded as medical history. Any new or worsening abnormalities at Visit 6/EOT (and subsequent visits, if applicable) will be recorded as AEs. Directed physical exams will be performed at subsequent follow-up visits until the finding has resolved or stabilized in the opinion of the investigator. *Vital Signs* Vital signs including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate will be measured at Visit 1/Screening, Visit 2/Baseline, and Visit 6/EOT. Assessments will also be performed at any subsequent follow-up visits if the results from the preceding visit are materially abnormal and clinically significant in the opinion of the investigator. Assessments will be made after the subject has rested in a seated position for at least five minutes. Height and weight will only be measured at Visit 1/Screening. *Clinical Laboratory Tests* Urine and blood samples will be collected from each subject for safety laboratory analysis at Visit 1/Screening and Visit 6/EOT. Clinical laboratory tests will also be performed at any subsequent follow-up visits if the results from the preceding visit are materially abnormal and clinically significant in the opinion of the investigator. Any new or worsening clinically significant abnormalities at Visit 6/EOT (and subsequent visits, if applicable) will be recorded as AEs. *Urine Pregnancy Tests* A UPT will be performed at Visit 1/Screening, Visit 2/Baseline, and Visit 6/EOT for WOCBP. *Local Skin Reactions* LSRs (burning/stinging, edema, and folliculitis) will be assessed at every visit (except Visit 1/Screening) using a 4-point ordinal scale (0=none, 1=mild, 2=moderate, 3=severe). Only LSRs that require medical intervention (e.g., prescription medication) will be documented as AEs. Any LSRs that are not listed above will be recorded as AEs.
Study Endpoints	Efficacy Endpoints: For each endpoint listed below the change from Baseline will be calculated for each treatment at Visits 3, 4, 5, 6, 7, 8, and 9 and summarized. Besides

	the change from Baseline, for each endpoint listed below, the within subject difference in the change scores between DUR-928 and VEH will also be calculated at each visit and summarized as the proportion of subjects in which DUR-928 is better than VEH, DUR-928 is the same as VEH, and DUR-928 is worse than VEH. 1. IGA Score. 2. Clinical Signs of Psoriasis (plaque elevation, scaling, and erythema). 3. LPSI (as a sum of all three parameters including plaque elevation, scaling, and erythema). 4. Target Plaque Area (will only be calculated at Visits 4, 6, and 9). 5. NRS for Pruritus (will only be calculated at Visits 4, 6, and 9). Treatment success outcomes will also be calculated and summarized as follows for each treatment at Visits 3, 4, 5, 6, 7, 8, and 9. 1. IGA – proportion of subjects with Target Plaques achieving a score of 0 or 1 representing "clear" or "almost clear" with at least 2-grade decrease in severity relative to Baseline. 2. Clinical Signs of Psoriasis – for each clinical sign (plaque elevation, scaling, erythema) the proportion of subjects with Target Plaques achieving a score of 0 or 1 representing "clear" or "almost clear" with at least 2-grade decrease in severity relative to Baseline. 3. NRS for Pruritus – proportion of subjects with Target Plaques that have a Baseline NRS score $\geq$ 4 and at least a 4 point decrease in NRS score relative to Baseline (will only be calculated at Visits 4, 6, and 9). 4. Target Plaque Area – proportion of subjects with Target Plaques achieving a 50% reduction in Target Plaque Area from Baseline (will only be calculated at Visits 4, 6, and 9). Additionally, Target Plaque Comparison score results will be summarized at Visits 2, 3, 4, 5, 6, 7, 8, and 9 as the proportion of subjects with each score including, 1A = Target Plaque A is better than Target Plaque B, 0 = Target Plaque A is the same as Target Plaque B, and 1B = Target Plaque A is worse than Target Plaque B. <u>Safety Endpoints:</u> 1. Incidence (severity and causality) of any local and systemic AEs. 2. Number of subjects with presence (and severity) of the following LSRs: burning/stinging, edema, and folliculitis at each time point (except Screening). 3. Changes from Baseline in vital signs at Visit 6/EOT (and subsequent visits, if applicable). 4. Changes from Screening in clinical laboratory tests (chemistry, hematology, and urinalysis) at Visit 6/EOT (and subsequent visits, if applicable). <u>Photography</u> Photographs taken by the sites only shall be used as supportive documentation of efficacy and safety outcomes for this study. An independent photo review may be performed at the discretion of the Sponsor.

Sample Size Calculations	This is a pilot, proof of concept study, therefore, no formal sample size calculations were performed for this study.
Statistical Methods	All statistical processing will be performed using SAS®. Summary tables (descriptive statistics and/or frequency tables) will be provided for Screening and/or Baseline variables, efficacy variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, median, standard deviation [SD], minimum, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data. Summaries will be provided for each treatment group. **Study Populations:** The Safety population will include all randomized subjects who received and applied test article. The intent-to-treat (ITT) population will include all randomized subjects who were dispensed the test article. The per-protocol (PP) population will include a subset of the ITT population who completed the study without significant protocol deviations (as will be determined prior to unblinding the randomization). **Efficacy Analyses:** The efficacy analyses will be conducted on the ITT and PP populations. For endpoints of change from Baseline, the comparison between DUR-928 and VEH will be conducted using a paired t-test with a significant alpha level of 0.05. For endpoints of treatment success outcomes, the comparison between DUR-928 and VEH will be conducted using McNemar's test with a significant alpha level of 0.05. The within subject difference in the change scores and Target Plaque Comparison score between DUR-928 and VEH will also be calculated and summarized descriptively. <u>Dosing Compliance</u> Descriptive statistics will be used to summarize for each treatment group the duration of treatment (defined as last dose date – first dose date +1), the total number of applications (determined from the doses reported in the Subject Diary), and the percent of expected doses applied for the ITT and PP populations. Subjects who apply at least 70% of the expected total number of applications and have no other evidence of material dosing non-compliance will be considered to be compliant with test article dosing. **Safety Analyses:** The safety analyses will be conducted on the Safety population. Safety endpoints will be summarized by descriptive statistics including sample size, mean, SD, median, minimum, and maximum; or by frequency and percentage as appropriate.

	Extent of Exposure Descriptive statistics will be used to summarize the extent of exposure. The total amount of test article used by each subject (prescribed amount of test article multiplied by the number of doses applied) and the mean daily amount of test article applied (total amount of test article applied divided by the duration of treatment) will be calculated. Physical Examinations Findings from physical examinations (head and neck, cardiovascular, dermatological, respiratory, gastrointestinal (abdomen), and gross motor and gait) will be recorded in medical history (from assessment at Visit 1/Screening) or as AEs (from assessment at Visit 6/EOT [and subsequent visits, if applicable]). Vital Signs Descriptive statistics of vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) at Visit 1/Screening, Visit 2/ Baseline, and Visit 6/EOT (and subsequent visits, if applicable) will be provided by treatment group. Clinical Laboratory Tests Clinical laboratory tests will be evaluated for any material changes during the study period. All laboratory data (hematology, chemistry, and urinalysis) will be listed and reported in the units received by the laboratory. Shift tables by analyte and by out of range flag will be presented to facilitate the evaluation of change from Visit 1/Screening to Visit 6/EOT (and subsequent visits, if applicable). Local Skin Reactions LSRs (burning/stinging, edema, and folliculitis) will be summarized by frequency of each individual LSR for each treatment group. Adverse Events All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the test articles, and outcome. Verbatim terms on the electronic case report forms (eCRFs) will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) mapping system. The PTs and SOC will then be tabulated. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article by treatment group. Urine Pregnancy Tests Results from UPTs (if applicable) at Visit 1/Screening, Visit 2/Baseline, and Visit 6/EOT will be provided in a listing.

CCI



CCI

ABBREVIATIONS

25HC	25-hydroxycholesterol
25HC3S	5-cholesten-3β, 25-diol 3-sulfate
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
β-hCG	Beta-Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
cm	Centimeter
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
g	Gram
GGT	Gamma-Glutamyltransferase
IB	Investigator Brochure
IFN-γ	Interferon-Gamma
IGA	Investigator's Global Assessment
IL-1β	Interleukin-1beta
IL-6	Interleukin-6
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
L	Left
LDH	Lactate Dehydrogenase
LPSI	Local Psoriasis Severity Index
LSR	Local Skin Reaction
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mIU	Milli International Units
NF	National Formulary
NRS	Numeric Rating Scale
OTC	Over-The-Counter
PP	Per-Protocol
PT	Preferred Term

R	Right
RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width
SAE	Serious Adverse Event
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
P P	
TNF-α	Tumor Necrosis Factor-alpha
UPT	Urine Pregnancy Test
USP	United States Pharmacopeia
VEH	Vehicle
WBC	White Blood Cells
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

TABLE OF CONTENTS

CCI [redacted]

[redacted]

3. OBJECTIVE

The primary objective of this trial is to determine and compare the safety, tolerability, and efficacy of DUR-928 with that of the vehicle control in subjects with plaque psoriasis with occlusion.

4. STUDY DESIGN

This is a multicenter, randomized, double-blind, vehicle-controlled, paired-plaque, proof of concept comparison study of DUR-928 in subjects with stable mild to moderate plaque psoriasis. Eligible subjects must have two similar contralateral Target Plaques as described in Section 5.1.1. Approximately 20 subjects will be enrolled at approximately three study sites to obtain about 15 evaluable subjects. The maximum proportion of subjects to be enrolled with mild plaque psoriasis is approximately 25% of the total enrolled subjects.

Each subject will receive both of the following treatments with occlusion:

1. DUR-928 Topical Solution, CC and
2. Vehicle Topical Solution

Subjects will be instructed to apply the test articles once daily to the two Target Plaques at approximately the same time and follow the instructions for application and occlusion. Subjects will be allowed to use triamcinolone cream, 0.1% and/or over the counter (OTC) hydrocortisone ointment or cream 1% or 0.5% on the face/neck, trunk, buttocks, and lower extremities only no more than twice daily. Subjects will also be allowed to use a bland emollient on all areas (face/neck, trunk, buttocks, lower extremities, upper extremities) that are not designated Target Plaques no more than twice daily. There will be nine study visits. Efficacy will be measured through Investigator's Global Assessment (IGA), Clinical Signs and Symptoms of Psoriasis including Local Psoriasis Severity Index (LPSI), Target Plaque Area, and Target Plaque Comparison assessments by the investigator or designee in a blinded fashion. Efficacy will also be measured using the subject-assessed Numeric Rating Scale (NRS) for Pruritus. Safety will be measured by brief physical examinations, vital signs, clinical laboratory tests, urine pregnancy tests (UPTs, if applicable), local skin reactions (LSRs), and adverse events (AEs).

5. STUDY POPULATION

5.1 Subject Eligibility

To be included in the study, subjects must meet the following inclusion and none of the exclusion criteria.

5.1.1 Inclusion Criteria

1. Subject is a male or non-pregnant female 18 years of age or older.
2. Subject has provided written informed consent.

3. Subject has a clinical diagnosis of stable mild to moderate plaque psoriasis for at least two months.
4. Females must be post-menopausal[6], surgically sterile[7], or use an effective method of birth control.[8,9] Women of childbearing potential (WOCBP) must have a negative UPT[10] at Visit 2/Baseline.
5. Males (or their female partner) must agree to use an effective method of birth control throughout the study.
6. Subject has two similar contralateral Target Plaques that:
    - Are located on the upper extremities not including the palms, and
    - Must individually be a minimum of 6 cm^2 in area, a maximum of 64 cm^2 in area, and a similar size (both Target Plaques should ideally be the same size but one should not be more than about a third larger [e.g., 33%] than the smaller plaque), and
    - Must have the same IGA score of 2 or 3, and
    - Must have the same plaque elevation score of 2 or 3, and
    - Have a Target Plaque Comparison score of 0 (Target Plaque A=Target Plaque B), and
    - Are easily accessible for test article application by the subject or a reliable care provider.
7. Subject is willing and able to apply the test article(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study.
8. Subject, in the investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of the plaque psoriasis or exposes the subject to an unacceptable risk by study participation.

5.1.2 Exclusion Criteria

1. Subject is pregnant, lactating, or is planning to become pregnant during the study.
2. Subject has spontaneously improving or rapidly deteriorating plaque psoriasis.

---

[6] Defined as amenorrhea greater than 12 consecutive months in women 50 years of age and older.
[7] Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment), or bilateral oophorectomy.
[8] Effective forms of birth control include a) hormonal contraceptives [e.g., oral, transdermal, injectable, implantable, or vaginal ring] (see next footnote), b) intrauterine device (IUD) for at least one week prior to test article application, c) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], d) monogamous relationship with a partner who is sterile [e.g., vasectomy performed at least six months prior to study entry], or e) total abstinence for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.
[9] WOCBP taking hormonal therapy must be on treatment prior to study entry, continued per label, and must not change their dosing regimen during the study; treatment must be for (1) oral: at least one complete cycle (e.g., four to eight weeks); (2) transdermal, injectable (e.g., Depo-Provera), implantable, or vaginal ring (e.g., NuvaRing): at least one week.
[10] UPT must have a minimum sensitivity of 25 mIU ß-hCG/mL.

3. Subject has guttate, pustular, erythrodermic, inverse, or other non-plaque forms of psoriasis.
4. Subject has any skin pathology or condition that, in the investigator's opinion, could interfere with the evaluation of the test article or requires use of interfering topical, systemic, or surgical therapy.
5. Subject has psoriasis beyond the two Target Plaques that, in the investigator's opinion, could not be reasonably managed with only bland emollient, triamcinolone cream, 0.1%, or OTC hydrocortisone during the study.
6. Subject has used any systemic methotrexate, retinoids, systemic corticosteroids (including intralesional, intra-articular, and intramuscular corticosteroids), cyclosporine, tofacitinib, apremilast, or analogous products within 90 days prior to Visit 2/Baseline.
7. Subject has used any systemic immunomodulatory biologic therapy (i.e., FDA-approved or experimental therapy) within five half-lives of the biologic prior to Visit 2/Baseline. Published or documented half-life of the product provided by the commercial supplier or Sponsor should be used to establish this value.
8. Subject has used any phototherapy (including laser), photo-chemotherapy, or other forms of photo-based therapy for the treatment of their psoriasis within 30 days prior to Visit 2/Baseline.
9. Subject had prolonged exposure to natural or artificial sources of ultraviolet radiation within 30 days prior to Visit 2/Baseline or is intending to have such exposure during the study which, in the opinion of the investigator, is thought to modify the subject's disease.
10. Subject has used topical body (excluding the scalp) psoriasis therapy (including coal tar, anthralin, steroids, retinoids, and vitamin D analogs) within 14 days prior to Visit 2/Baseline.
11. Subject has undergone treatment with Vitamin A supplements within 14 days prior to Visit 2/Baseline.
12. Subject has used emollients/moisturizers on areas to be treated within four hours prior to clinical evaluation at Visit 2/Baseline.
13. Subject is currently using lithium or Plaquenil (hydroxychloroquine).
14. Subject is currently using a beta-blocking medication (e.g., propranolol) or angiotensin converting enzyme (ACE) inhibitor at a dose that has not been stabilized (i.e., on the same dosage for at least four weeks).
15. Subject has a history of cancer, with the exception of successfully treated non-metastatic basal cell and squamous cell carcinoma.
16. Subject is currently enrolled in an investigational drug or device study.
17. Subject has used an investigational drug or investigational device treatment within 30 days prior to Visit 2/Baseline.
18. Subject has been previously enrolled in this study and treated with test article.
19. Subject has a history of sensitivity to any of the ingredients in the test articles.
20. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.

5.1.3 Subject Withdrawal Criteria

Procedures for handling subjects who are discontinued from the study are described in Section 13.2. Subjects who are discontinued will be replaced to achieve approximately 20 subjects who complete the treatment.

6. TEST ARTICLES AND REGIMEN

6.1 Description

DUR-928 Topical Solution, CCI is a clear, colorless solution. Vehicle Topical Solution contains the same excipients and has the same appearance as the active formulation.

Test Article #1:	DUR-928 Topical Solution, CCI
Active ingredient:	5-cholesten-3β, 25-diol 3-sulfate
Other ingredients:	CCI

Test Article #2:	Vehicle Topical Solution
Active ingredient:	None
Other ingredients:	CCI

6.2 Instructions for Use and Application

At Visit 2/Baseline, subjects will be instructed on how to apply the test articles and will apply the first test article applications and perform occlusion at the site under supervision of the study staff. The volume applied to each Target Plaque will remain fixed over the four week treatment period and will be determined based on plaque size (rounded off to the nearest whole number) according to the following table:

CCI

These volumes should allow for a good uniform coat of the test article to be applied to the entire lesion, CCI around the Target Plaque. The appropriate amount of test article will be withdrawn from the vial CCI and applied to the plaque. Subjects will be trained on using the syringe to withdraw test article and apply to the plaques. CCI is easy to apply and therefore may lead to under treatment. This is particularly true for plaques with heavy scaling where inadequate dosing of test article may result in a limited amount of test article being applied just to the top of scales on the plaque rather than to the entire Target Plaque. Be sure to instruct subjects to check for complete application to the Target Plaque itself as well as any scaling. Subjects will be instructed to apply the test articles once daily to the Target Plaques at approximately the same time. CCI . Subjects will also be instructed to take a photograph of the Treatment Area each day during the occlusive period for compliance review by the study staff at clinic visits. Triamcinolone cream, 0.1% will be provided to treat plaques that are located on the CCI . In addition, subjects may use OTC hydrocortisone ointment or cream 1% or 0.5% to treat plaques that are located on the CCI ; subjects may purchase this at their local pharmacy or store as directed by the investigator. A bland emollient will also be provided to treat plaques that are not designated Target Plaques no more than twice daily.

NOTE: Since this is a bilateral comparison study of active versus vehicle it is important the subject correctly applies the same product to the same Target Plaque over the four week treatment period. The test article vials are color-coded and labeled according to which Target Plaque they are to be applied. In all cases, use of the term LEFT or RIGHT, is in reference to the subject's left or right, not the evaluator's.

White LABEL=Target Plaque A (Left)
Yellow LABEL=Target Plaque B (Right)

To minimize errors, at each clinic visit during the treatment period the site must review and emphasize the proper application of the test article.

Subjects will be provided with a Subject Instruction Sheet detailing how to apply the test articles and perform occlusion (CCI) and a Subject Diary (CCI) to record dates and times of applications and occlusion. Subjects will be instructed to bring all test article containers (used and unused) and the Subject Diary to the study visits. At the appropriate study visits, Subject Diary will be collected, reviewed, and a new one will be dispensed to the subject (as needed). Subjects will be instructed to store the test articles according to the directions on the label.

6.3 Warnings, Precautions, and Contraindications

These test articles are for topical use only. Care should be taken to avoid contact with eyes and all mucous membranes. If contact with eyes occurs, rinse thoroughly with water.

Subjects with a known sensitivity to any of the ingredients in the test articles should not participate in this study.

Should skin irritation or rash develop, discontinue use and contact the investigator.

In case of accidental ingestion, subjects should contact the investigator immediately.

Keep test articles out of reach of children/pets.

The effects of the test article in nursing mothers, pregnant women, and their unborn children are unknown. WOCBP must not be pregnant or planning a pregnancy during the study period.

7. RANDOMIZATION ASSIGNMENT

At Visit 2/Baseline, each eligible subject will be randomized by assigning the lowest available test article kit number. Subjects will be dispensed both test articles that will be blinded using labels that are white versus yellow. The assignment of treatments for Target Plaque A and Target Plaque B are described in Section 9.1.

8. PRIOR AND CONCOMITANT THERAPIES

Current medications and any medications taken within 30 days prior to the start of the study (Visit 2/Baseline) will be recorded as prior/concomitant medications with the dose and corresponding indication. The medications to be recorded include prescription, over-the-counter medications, and vitamins, minerals, and dietary supplements being taken for a therapeutic indication. All medications taken on a regular basis must be recorded on the electronic case report forms (eCRFs). All concomitant medications will be coded with the current version of the WHO Drug Dictionary.

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Non-prohibited chronic therapies being used at Visit 2/Baseline may be continued, but must be recorded.

Any changes in concomitant medications and/or therapies/procedures during the study must be recorded. The reason for any changes in concomitant medications and/or therapies/procedures should be reported and should reflect either a baseline medical condition documented in the medical history or in conjunction with an AE.

8.1 Prohibited Medications or Therapies

Prior to entry in the study or during the course of the study, subjects must not use the medications or procedures within the time frame prior to randomization as specified in Section 5.1.2. Subjects may washout from prohibited medications or treatments for plaque psoriasis. The following medications and procedures/therapies are prohibited during the study from Visit 2/Baseline through Visit 9/End of Study (EOS).

- Any systemic methotrexate, retinoids, systemic corticosteroids (including intralesional, intra-articular, and intramuscular corticosteroids), cyclosporine, tofacitinib, apremilast, or analogous products
- Any systemic immunomodulatory biologic therapy (i.e., FDA-approved or experimental therapy)
- Any phototherapy (including laser), photo-chemotherapy, or other forms of photo-based therapy for the treatment of their psoriasis
- Prolonged exposure to natural or artificial sources of ultraviolet radiation
- Topical body (excluding the scalp) psoriasis therapy (including coal tar, anthralin, steroids [with the exception of triamcinolone and hydrocortisone specified in Section 8.2], retinoids, and vitamin D analogs)
- Treatment with Vitamin A supplements
- Emollients/moisturizers on either Target Plaque
- Current use of lithium or Plaquenil (hydroxychloroquine)
- Current use of a beta-blocking medication (e.g., propranolol) or ACE inhibitor at a dose that has not been stabilized (i.e., on the same dosage for at least four weeks)
- Any investigational drug or investigational device treatment

8.2 Allowed Medications or Therapies

Effective methods of contraception for WOCBP are required per Inclusion Criterion #4. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health, but must be recorded if taken for a therapeutic indication. Non-prohibited chronic therapies being used at Visit 1/Screening may be continued.

Sunscreens are discouraged during the study given they can potentially affect skin disease. Ideally protective clothing (e.g., hat, long sleeve shirts) is recommended. Nonetheless, when extenuating circumstances warrant sunscreen use, it may be used but should be recorded as a concurrent therapy if applied on the upper extremities. If sunscreen is applied on the upper extremities, application to the regions of the Target Plaques should ideally be avoided, if at all possible.

Triamcinolone cream, 0.1% in addition to OTC hydrocortisone ointment or cream 1% or 0.5% as directed by the investigator will be allowed no more than twice daily to treat plaques that are located on the CCI [redacted]. Note: the availability of a Group 4 (triamcinolone) and Group 7 (hydrocortisone) corticosteroid

will provide the investigator with some options to treat intertriginous, facial, and body areas as he/she sees fit.

The use of bland emollients is allowed to treat all areas of plaque psoriasis EXCEPT on Target Plaques no more than twice daily.

9. STUDY PROCEDURES

9.1 Identification and Labeling of Target Plaques

The location and identification of the two Target Plaques selected for treatment will be recorded on the body diagram source document. The involvement (Yes/No) of the elbow will also be recorded at Visit 1/Screening and Visit 2/Baseline. At Visit 2/Baseline, photographs will be taken to document the location of the Target Plaques. These plaques will be labeled as Target Plaque A and B. In addition to these labels, each Target Plaque will be accompanied by an anatomic descriptor that refers to the location on the subject's body (e.g., Target Plaque A will be labeled LEFT ARM and Target Plaque B will be labeled RIGHT ARM).

NOTE: in all cases, use of the term LEFT or RIGHT, is in reference to the subject's right or left, not the evaluator's.

The identification, location, and the assigned treatment of the Target Plaques will be identified per the following table:

CCI

[redacted]

Specific activities for each study visit are listed below.

9.2 Visit 1 (Day -30 to -1): Screening

At Screening, the investigator or designee will:

- Obtain a signed, written informed consent.
- Record demographics.
- Confirm inclusion/exclusion criteria.
- Record medical history.
- Record prior and/or concomitant medications and procedures/therapies.

- Perform a brief physical exam. Record abnormalities in medical history. See Section 10.2.1
- Measure vital signs (including height and weight). See Section 10.2.2.
- Perform a UPT for all WOCBP. The results must be negative for the subject to be enrolled.
- Collect urine and blood samples for clinical laboratory tests (chemistry, hematology, and urinalysis). Subjects must be fasting for approximately eight hours.
- Identify Target Plaques. See Inclusion Criterion #6 in Section 5.1.1 and Section 9.1.
- Perform clinical evaluations (IGA, Target Plaque Area, Clinical Signs of Psoriasis including LPSI, and Target Plaque Comparison) of Target Plaques. See Section 10.1.
- Schedule the Visit 2/Baseline visit.

9.3 Visit 2 (Day 1): Baseline

At Baseline, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and procedures/therapies, and document the findings.
- Reconfirm all inclusion/exclusion criteria, including identification of the Target Plaques. If the subject meets all inclusion criteria and no exclusion criteria, continue with the remaining Visit 2/Baseline procedures.
- Measure vital signs. See Section 10.2.2.
- Perform a UPT for all WOCBP. The results must be negative for the subject to continue in the study.
- Perform photography of the Target Plaques.
- Perform clinical evaluations (IGA, Target Plaque Area, Clinical Signs of Psoriasis including LPSI, and Target Plaque Comparison) of Target Plaques. See Section 10.1.
- Have subject perform NRS for Pruritus prior to first application of test article. See Section 10.1.5.
- Assess LSRs prior to first application of test article. See Section 10.2.3.
- Randomize the subject by assigning the next available (lowest) test article kit number.
- Dispense Subject Instructions ([redacted]).
- Dispense the Subject Diary ([redacted]).
- Document Test Article Accountability and dispense the test articles, as applicable.
- Supervise the application of the test articles and instruct the subject to record the date and time in the Subject Diary.
- Assess LSRs 15 minutes after the first application of test articles. See Section 10.2.3.
- Supervise the occlusion of the Target Plaques and instruct the subject to record the time in the Subject Diary. For the first test article application only, occlusion will begin 15 minutes after test article application so that LSRs can be assessed.

- Document any AEs.
- Schedule the next visit.

9.4 Visit 3 (Day 8 ± 1): Week 1, Visit 4 (Day 15 ± 2): Week 2, and Visit 5 (Day 22 ± 2): Week 3

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and procedures/therapies, and document the findings.
- Perform photography of the Target Plaques.
- Perform clinical evaluations (IGA, Clinical Signs of Psoriasis including LPSI, and Target Plaque Comparison) of Target Plaques. See Section 10.1.
- **Visit 4 only:** Have subject perform NRS for Pruritus (see Section 10.1.5) and Target Plaque Area (see Section 10.1).
- Assess LSRs. See Section 10.2.3.
- Review and dispense (as necessary) Subject Instructions, (CCI [redacted]) **and review proper use of the correct test article for each of the two Target Plaques**.
- Review compliance, check subject photos as additional confirmation of proper occlusion, and collect/dispense the Subject Diary, as applicable (CCI [redacted]).
- Document Test Article Accountability and collect/dispense the test articles, as applicable.
- Document any AEs.
- Schedule the next visit, as appropriate.

9.5 Visit 6 (Day 29 + 3): Week 4/End of Treatment

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and procedures/therapies, and document the findings.
- Perform a brief physical exam. Record any new or worsening abnormalities as an adverse event. See Section 10.2.1.
- Measure vital signs. See Section 10.2.2.
- Perform a UPT for all WOCBP.
- Collect urine and blood samples for clinical laboratory tests (chemistry, hematology, and urinalysis). Subjects must ideally be fasting for approximately eight hours.
- Perform photography of the Target Plaques.
- Perform clinical evaluations (IGA, Target Plaque Area, Clinical Signs of Psoriasis including LPSI, and Target Plaque Comparison) of Target Plaques. See Section 10.1.
- Have subject perform NRS for Pruritus. See Section 10.1.5.
- Assess LSRs. See Section 10.2.3.
- Review compliance, check subject photos as additional confirmation of proper occlusion, and collect the Subject Diary.

- Document Test Article Accountability and collect all test articles, as applicable.
- Document any AEs.
- Schedule the follow-up visit.

9.6 Visit 7 (Day 36 ± 3): Follow-up 1

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and procedures/therapies, and document the findings.
- Perform a directed physical exam (only if Visit 6/EOT results are materially abnormal and clinically significant). Record any new or worsening abnormalities as an adverse event. See Section 10.2.1.
- Measure vital signs (only if Visit 6/EOT results are materially abnormal and clinically significant). See Section 10.2.2.
- Collect urine and blood samples for clinical laboratory tests (chemistry, hematology, and urinalysis) (only if Visit 6/EOT results are materially abnormal and clinically significant). Subjects should ideally be fasting for approximately eight hours.
- Perform photography of the Target Plaques.
- Perform clinical evaluations (IGA, Clinical Signs and Symptoms of Psoriasis including LPSI, and Target Plaque Comparison) of Target Plaques. See Section 10.1.
- Assess LSRs. See Section 10.2.3.
- Document any AEs.
- Schedule the follow-up visit.

9.7 Visit 8 (Day 50 ± 3): Follow-up 2

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and procedures/therapies, and document the findings.
- Perform a directed physical exam (only if Visit 7 results are materially abnormal and clinically significant). Record any new or worsening abnormalities as an adverse event. See Section 10.2.1.
- Measure vital signs (only if Visit 7 results are materially abnormal and clinically significant). See Section 10.2.2.
- Collect urine and blood samples for clinical laboratory tests (chemistry, hematology, and urinalysis) (only if Visit 7 results are materially abnormal and clinically significant). Subjects should ideally be fasting for approximately eight hours.
- Perform photography of the Target Plaques.
- Perform clinical evaluations (IGA, Clinical Signs and Symptoms of Psoriasis including LPSI, and Target Plaque Comparison) of Target Plaques. See Section 10.1.

- Assess LSRs. See Section 10.2.3.
- Document any AEs.
- Schedule the EOS visit.

9.8 Visit 9 (Day 57 ± 3): End of Study

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and procedures/therapies, and document the findings.
- Perform a directed physical exam (only if Visit 8 results are materially abnormal and clinically significant). Record any new or worsening abnormalities as an adverse event. See Section 10.2.1.
- Measure vital signs (only if Visit 8 results are materially abnormal and clinically significant). See Section 10.2.2.
- Collect urine and blood samples for clinical laboratory tests (chemistry, hematology, and urinalysis) (only if Visit 8 results are materially abnormal and clinically significant). Subjects should ideally be fasting for approximately eight hours.
- Perform photography of the Target Plaques.
- Perform clinical evaluations (IGA, Target Plaque Area, Clinical Signs and Symptoms of Psoriasis including LPSI, and Target Plaque Comparison) of Target Plaques. See Section 10.1.
- Have subject perform NRS for Pruritus. See Section 10.1.5.
- Assess LSRs. See Section 10.2.3.
- Document any AEs.
- Exit the subject from the study.

10. CLINICAL EVALUATIONS

The following clinical evaluations will be performed according to the schedules indicated during the study. The same investigator should complete the evaluations for a given subject throughout the study. If this is not possible (e.g., scheduling conflict), a different expert grader with overlapping experience with the subject and the study should complete the evaluations.

10.1 Efficacy Evaluations

10.1.1 Investigator's Global Assessment

The IGA score is a static evaluation of the overall or "average" degree of severity of each of the two Target Plaques by the investigator or designee as the subject appears on the day of evaluation. This evaluation takes into consideration the three individual characteristics of psoriasis (plaque elevation, scaling, and erythema) with the IGA score at each visit representing the average of plaque elevation, scaling, or erythema that is present amongst

the two Target Plaques. IGA will be assessed individually for the two Target Plaques on a 5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe.

The investigator should NOT refer to any other assessments to assist with this evaluation. This evaluation is NOT a comparison with the IGA at any other visit or a mathematical calculation based on the clinical signs of psoriasis scores. The Visit 2 assessment must be made PRIOR to the first application of the test articles and subsequent assessments should be made four hours or more after any application of the test article.

At every study visit, both Target Plaques will be evaluated individually and the one whole integer score will be documented that describes the average IGA for each Target Plaque using the following scale:

CLEAR (0)
Scaling: no evidence of scaling
Erythema: no evidence of erythema (except possible residual discoloration)
Plaque Elevation: no evidence of plaque elevation above normal skin level

ALMOST CLEAR (1)
Scaling: limited amount of very fine scale
Erythema: light pink color dominates over all or part of the plaque
Plaque Elevation: very slight elevation above normal skin level, easier felt than seen

MILD (2)
Scaling: mainly fine scales; plaque is partially covered
Erythema: light red to pink dominates over all or part of the plaque
Plaque Elevation: slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped over most of the plaque

MODERATE (3)
Scaling: somewhat coarser scales; a significant portion or all of the plaque is covered
Erythema: red dominates over all or part of the plaque
Plaque Elevation: moderate elevation with rounded or sloped edges on most of the edges of the plaque

SEVERE (4)

Scaling: coarse, thick scales; virtually all of the plaque is covered; rough surface
Erythema: virtually all of the plaque is bright to dusky red
Plaque Elevation: marked to very marked elevation, with hard to very hard sharp edges on virtually all edges of the plaque

10.1.2 Target Plaque Area

The surface area of each of the two Target Plaques will be determined by tracing the border of each Target Plaque CCI and then totaling the area contained within the border. Each Target Plaque must individually be CCI .

10.1.3 Clinical Signs of Psoriasis and Local Psoriasis Severity Index

Plaque elevation (induration), scaling, and erythema will each be scored on a 5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. These evaluations are an assessment of the overall or "average" degree of each of three key characteristics present within each of the two Target Plaques by the investigator or designee as the subject appears on the day of the evaluation and will be assessed individually for each Target Plaque. **The investigator should NOT refer to any other evaluations to assist with this assessment.** The Visit 2 assessment must be made PRIOR to the first application of the test article (for Target Plaques only), bland emollient (for areas that are not designated Target Plaques), and triamcinolone cream, 0.1% or OTC hydrocortisone (CCI). Subsequent assessments should be made four hours or more after any application of the test article. At every study visit, the investigator or designee will evaluate both Target Plaques individually and report the one whole integer score that describes the average severity for each clinical sign of psoriasis using the following scales:

Plaque Elevation:

0	Clear	No evidence of plaque elevation above normal skin level.
1	Almost clear	Very slight elevation above normal skin level, easier felt than seen.
2	Mild	Slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped, on some of the plaques.
3	Moderate	Moderate elevation with rounded or sloped edges on most of the edges of the plaque.
4	Severe	Marked to very marked elevation with hard to very hard sharp edges on virtually all edges of the plaque.

Scaling:

0	Clear	No evidence of scaling.
1	Almost clear	Limited amount of very fine scale.
2	Mild	Mainly fine scales; plaque is partially covered.
3	Moderate	Somewhat coarser scales; a significant portion or all of the plaque is covered.
4	Severe	Coarse, thick scales; virtually all of the plaque is covered; rough surface.

Erythema:

0	Clear	No evidence of erythema (except possible residual discoloration).
1	Almost clear	Light pink color dominates over all or part of the plaque.
2	Mild	Light red to pink dominates over all or part of the plaque.
3	Moderate	Red dominates over all or part of the plaque.
4	Severe	Virtually all of the plaque is bright to dusky red.

The LPSI is defined as the sum of scoring for plaque elevation, scaling, and erythema. LPSI will range from 0 to 12, with the highest score representing the more severe disease state.

10.1.4 Target Plaque Comparison Score

The overall appearance of the two individual Target Plaques will be evaluated as follows: Target Plaque A is better than Target Plaque B, Target Plaque A is the same as Target Plaque B, or Target Plaque A is worse than Target Plaque B. This evaluation will not be a comparison with the condition at a previous visit, but a comparison of the two Target Plaques to determine which one appears better than the other. Note: The two plaques may have identical IGA scores but still be different based upon the comparison score.

Score	Comparison
1A	Target Plaque A is better than Target Plaque B
0	Target Plaque A is the same as Target Plaque B
1B	Target Plaque A is worse than Target Plaque B

10.1.5 Numeric Rating Scale for Pruritus

Pruritus will be assessed using the Itch Numeric Rating Scale (I-NRS), a self-administered Patient Reported Outcome questionnaire [10]. Subjects will indicate itch severity for each Target Plaque by circling the integer that best describes the worst level of itching due to psoriasis in the past 24 hours on an 11-point scale anchored at 0, representing "no itching" and 10, representing, "worst itch imaginable" (CCI [redacted]). The study staff should review the NRS for Pruritus with each subject and ask them to indicate the response that best describes their experience. Pruritus assessed by this evaluation should be reported as an AE only if therapy is required.

10.2 Safety Evaluations

10.2.1 Brief Physical Examination

A brief physical exam will be performed at Visit 1/Screening and Visit 6/EOT. The exam will include examination of head and neck, dermatological, cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait. Abnormalities at Visit 1/Screening will be recorded as medical history. Any new or worsening abnormalities at Visit 6/EOT (and subsequent visits, if applicable) will be recorded as AEs. Directed physical exams will be performed at subsequent follow-up visits until the finding has resolved or stabilized in the opinion of the investigator.

10.2.2 Vital Signs

Vital signs including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate will be measured at Visit 1/Screening, Visit 2/Baseline, and Visit 6/EOT. Assessments will also be performed at any subsequent follow-up visits if the results from the preceding visit are materially abnormal and clinically significant in the opinion of the investigator. Assessments will be made after the subject has rested in a seated position for at least five minutes. Height and weight will only be measured at Visit 1/Screening.

10.2.3 Local Skin Reactions

LSRs (burning/stinging, edema, and folliculitis) will be assessed for each Target Plaque at every visit (except Screening) using a 4-point ordinal scale (0=none, 1=mild, 2=moderate, 3=severe). Only LSRs that require medical intervention (e.g., prescription medication) will be documented as AEs. Any LSRs that are not listed above will be recorded as AEs.

11. PHOTOGRAPHY

Photography documentation is required in this study. Photographs taken as part of this study will be used to document the effects of treatment, AEs, or other findings during the study. All subjects will be asked to consent to the collection of photographs of their Target Plaques. Digital photographic records of the two Target Plaques (A & B) will be generated for each plaque site before the first application of test article and at each subsequent visit. To help with treatment identification, each Target Plaque site will be marked by a specific label on the photographs taken. Photographs of test sites will be taken under identical conditions, as much as possible, to enable proper comparisons to be made as detailed in the Study Photo Guide. Photographs shall be used as supportive documentation of efficacy and safety outcomes for this study but are not to be used by the investigator for grading or for any other assessment. An independent photo review may be performed at the discretion of the Sponsor. Any photographs taken of readily identifiable features (e.g., the face) will be de-identified (i.e., a masking bar over the eyes). In addition, photographs may be taken at the discretion of the investigator at any time to document the subject's progress in the study, AEs, or other findings of note.

Note: Subjects who decline to have photographs taken during the conduct of study may not participate in the study given that photography is required. If a subject initially consents to photographs, then declines further photography, the Sponsor may use the photographs taken under consent for the purposes noted above.

Subjects will also be instructed to take daily photographs of the treatment area during the occlusion step. At each visit, the daily photographs will be reviewed by the study staff to support compliance only. Daily photographs will not be collected or used as supportive documentation of efficacy or safety outcomes for this study.

12. LABORATORY TESTS

12.1 Blood Chemistries, Hematology, and Urinalysis

Urine and blood samples will be collected from each subject for safety laboratory analysis at Visit 1/Screening and Visit 6/EOT; clinical laboratory tests will also be performed at any subsequent follow-up visits if the results from the preceding visit are materially abnormal and clinically significant in the opinion of the investigator. Subjects must be fasting (approximately 8 hours) for Visit 1/Screening and, if possible, for Visit 6/EOT (and subsequent visits, if applicable); however, if a subject arrives at the clinic for Visit 6/EOT (or subsequent visits, if applicable) without fasting for at least eight hours, laboratory specimens may be collected as non-fasting, at the discretion of the investigator, and with the appropriate fasting status documented on the lab requisition form. Any new or worsening clinically significant abnormalities at Visit 6/EOT (and subsequent visits, if applicable) will be recorded as AEs. At the discretion of the investigator, clinical laboratory tests can be conducted at additional visits.

The following laboratory tests will be performed:

CCI

Sample collection, handling, labeling, and shipping should be done following the instructions provided by the relevant certified laboratory and the applicable local regulations.

The investigator must review all the subject's laboratory reports in a timely manner. **NOTE**: The investigator will initial and date each laboratory report to indicate his/her review. The investigator will note, directly on the laboratory report, whether or not any abnormal test results are clinically significant or not clinically significant. Clinical significant laboratory abnormalities that are present at Screening and/or Baseline must be documented in the subject's medical history. In addition, the investigator must complete an appropriate AE form for any new or worsening abnormal test results that are identified as clinically significant after Baseline.

AEs that may be associated with venipuncture and that must be included in the informed consent include:

- Pain
- Bruising
- Bleeding at the puncture site
- Fainting
- Inflammation of the vein

12.2 Urine Pregnancy Tests

A UPT will be performed at Visit 1/Screening, Visit 2/Baseline, and Visit 6/EOT for WOCBP.

The UPTs will be performed at the study site, if the site is registered and conforms to Clinical Laboratory Improvement Amendments (CLIA) regulations for such testing (possesses a current valid CLIA Certificate of Waiver), or at an appropriately registered reference laboratory. The investigator will report the UPT results on the eCRFs, in the subject's medical records, and in independent records maintained at the study site. The UPT used must have a minimum sensitivity of 25 mIU of β-hCG/mL.

13. END OF STUDY CRITERIA

At the end of each subject's participation in the study, the investigator will complete an End of Study Disposition form for all completed and discontinued subjects.

13.1 Completion of the Study

Subjects who complete the four-week course of treatment as specified in this protocol and return for Visit 9/EOS will be considered to have completed the study.

13.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

- AEs
- Death
- Lack of efficacy (defined as the lack of expected or desired effect related to a therapy)
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Progressive disease (defined as a disease process that is increasing in extent or severity)
- Protocol deviation
- Study terminated by Sponsor

- Withdrawal by subject; NOTE: if the subject decides to withdraw from the study due to an AE then it should be classified as withdrawal due to an AE
- Other (e.g., any reason that may affect the outcome of the study or safety of subjects)

If a subject withdraws from the study prematurely for any reason, the site should make every effort to have the subject return to the clinic to perform all of the required visit activities for Visit 6 if the subject is withdrawing during the treatment phase of the study or Visit 9 if the subject is in the post-treatment follow-up phase of the study and to collect and reconcile all test articles (if applicable). If the subject will not return to the clinic, the site should make every attempt to contact the subject; otherwise the subject will be considered lost to follow-up.

When a subject is withdrawn from the study for a test article related AE (as defined in Section 14.2), when possible, the subject should be followed until resolution or stabilization of the AE. If the subject is discontinued from the study due to pregnancy, the pregnancy and its outcome should be followed.

Subjects who are prematurely withdrawn or discontinued from the study will be replaced until approximately 20 subjects have completed the study.

13.3 Study Termination

The study may be terminated by the investigator or the Sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, he or she may stop the study. A study termination by the investigator will be reported to the Sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the Sponsor by the investigator within five working days.

In the event that the Sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

14. ADVERSE EVENT REPORTING

14.1 Adverse Event Definitions

An **adverse event** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of

the drug (e.g., off-label use, use in combination with any drug) and from any route of administration, formulation, or dose, including an overdose.

A **suspected adverse reaction** is any AE for which there is a reasonable possibility that the drug caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. For the purposes of prescription drug labeling, the term adverse reaction means an undesirable effect, reasonably associated with the use of a drug that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, the event is considered "unexpected" if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Timely and complete reporting of all AEs assists the Sponsor and/or their designee in identifying any untoward medical occurrence, thereby allowing:

1) protection of the safety of study subjects;
2) a greater understanding of the overall safety profile of the test article;
3) recognition of dose-related test article toxicity;
4) appropriate modification of study protocols;
5) improvements in study design or procedures; and
6) adherence to worldwide regulatory requirements.

14.2 Adverse Event Details

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. All AEs must be recorded on the AE eCRF. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of test article or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. AEs should be followed to resolution or

stabilization (if possible) and, if they become serious, reported as serious adverse events (SAEs, see Section 14.3). If possible, the outcome of any AEs that caused permanent discontinuation or that were present at the end of the study, especially those considered by the investigator to be related to the test article, should be reported.

Information on the medical condition of subjects should begin following the subject's written informed consent to participate in the study and a medical history should be taken at screening. During any wash out and baseline periods, any changes in the health of subjects should be recorded as changes in medical history unless an event occurred as a result of a study-related procedure and is unanticipated; in such cases, the event should be recorded as an AE and reported to the Institutional Review Board (IRB) as an "unanticipated problem" in accordance with local procedures. Other changes in subject health information becomes AE data when the subject begins dosing with the test article; therefore AE data should be collected from the date of the first dose of test article until the date of the final study visit. These data are considered treatment-emergent AEs.

The investigator will instruct the subject to report any AEs that may occur during the study. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject's overall health status since the previous visit.

The severity of each AE, as judged by the investigator, will be recorded on the appropriate AE eCRF and will be graded according to the following scale:

> **Mild** - The AE is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
>
> **Moderate** - The AE is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
>
> **Severe** - The AE interrupts usual activities of daily living or significantly affects clinical status, or may require intensive therapeutic intervention.

The investigator must determine the relationship of the AE to the test article according to the following categories:

> **Definitely Related** - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage, and reappearance of the event on repeated exposure (re-challenge).
>
> **Probably Related** - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern

to the test article; and that is confirmed by improvement on stopping or reducing the dosage of the test article; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.

Possibly Related - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; but may have been caused by concurrent/underlying illness, other drug, procedure, or other causes.

Unlikely Related - An event that does not follow a reasonable temporal sequence from administration of the test article; that does not follow a known or expected response pattern to the test article, or most likely was caused by concurrent/underlying illness, other drug, procedure, or other causes, because of their known effects.

Not Related - An event almost certainly caused by concurrent/underlying illness, other drug, procedure, or other causes.

The investigator should categorize the outcome of the AE according to the following categories:

Fatal - Termination of life as a result of an AE.

Not Recovered/Not Resolved - AE has not improved or the subject has not recuperated.

Recovered/Resolved - AE has improved or the subject has recuperated.

Recovered/Resolved with Sequelae - subject recuperated but retained the pathological conditions resulting from the prior disease or injury.

Recovering/Resolving - AE is improving or the subject is recuperating.

Unknown - Not known, not observed, not recorded or subject refused.

14.3 Serious Adverse Event

An event that is serious must be recorded on the AE eCRF and on the P P SAE Report Form, and requires expeditious handling to comply with regulatory requirements.

An AE or suspected adverse reaction is considered “serious” if, in the opinion of either the investigator or Sponsor, it results in any of the following outcomes:

- Death; the event must be the cause of death for the SAE to meet this serious criterion.

- Life-threatening event; an event in which the subject was at risk of death at the time of the event and not an event that hypothetically might have caused death if it had been more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization (for ≥24 hours).
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical events; a medical event(s) that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events NOT considered to be SAEs are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen; and
- Treatment on an emergency, outpatient basis, for an event not fulfilling any of the definitions of "serious" given above and not resulting in hospital admission.

AEs classified as "serious" by either the investigator or the Sponsor require expeditious handling and reporting to P P to comply with regulatory requirements. **All SAEs, whether related or unrelated to test article, must be immediately reported by telephone to the Medical Monitor and, in the event that he/she is unavailable, to the Project Manager listed on the first page of the protocol.** Written notification of all SAEs should be sent to the Project Manager by email or confirmed facsimile transmission. These include those SAEs listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the test article caused the event.

Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the test article and the event (e.g., death from anaphylaxis). In this case, the investigator must immediately report the event to the Sponsor. In addition, such information should also be provided to the site's respective IRB per their governing guidelines for SAE reporting.

Any suspected adverse reactions that are serious and unexpected represent especially important safety information that must be reported more rapidly to Health Authorities; therefore, it is important that the investigator submit any information requested by the Sponsor or designee as soon as it becomes available.

If only limited information is initially available, follow-up reports are required. Should the investigator become aware of an SAE (regardless of its relationship to test article) that

occurs within 30 days after stopping the test article, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to PPD if available.

As required, the Sponsor will notify participating investigators of all suspected adverse reactions that are serious and unexpected. This notification will be in the form of an IND safety report of potential serious risks as soon as possible but no later than 15 calendar days after the Sponsor determines that the information is "reportable" according to the criteria listed in 21 CFR Section 312.32. These are:

i) Serious and unexpected suspected adverse reactions;
ii) Findings from other studies including epidemiological studies, pooled analyses, or other clinical studies that suggest a significant risk in humans exposed to the test articles;
iii) Findings from animal or in vitro tests that suggest a significant risk to humans exposed to the test articles, or reports of significant organ toxicity at or near the expected human exposure; and
iv) Clinically important increases in the rate of occurrence of serious suspected adverse reactions.

Upon receiving such notices, the investigator must review and retain the notice with the IB and promptly submit a copy of this information to the responsible IRB according to local regulations. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of safety updates by the investigator to Health Authorities should be handled according to local regulations.

The Sponsor or designee may be required to report certain SAEs to regulatory authorities (e.g., United States FDA) within seven calendar days of being notified about the event; therefore, it is important that investigators submit any information requested by the Sponsor or designee as soon as it becomes available.

14.4 Laboratory Test Abnormalities

Any clinically significant laboratory test result that meets the criteria for an AE (see Section 14.1) or SAE (see Section 14.3) must be recorded on the AE eCRF, in addition to being recorded on the appropriate laboratory test results eCRF and the original laboratory report, as applicable. In these cases, PPD will typically require additional information about the clinically significant abnormality, including information regarding relationship to test article, any action taken, and outcome. Clinically significantly laboratory abnormalities that qualify as SAEs must be reported to the Sponsor and IRB as per Section 14.3.

14.5 Pregnancy

WOCBP (see Schedule of Events for definition of WOCBP) must have a UPT prior to study enrollment. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during the study and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

WOCBP 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 a subject may be pregnant at any time during the study, the test article must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or apply further test article and must be discontinued from the study unless the Medical Monitor elects to retain the subject to follow the subject for safety only for all or part of the remaining study period.

If following initiation of study treatment, it is subsequently discovered that a subject was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the Medical Monitor of this event and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to PP D. The investigator must notify the IRB of any pregnancy associated with the study treatment and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated, including counseling of the subject by the investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the investigator must report to PP D. on the appropriate pregnancy surveillance form(s), any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs or SAEs (if they fulfill the SAE criteria). Offspring should be followed for a minimum of eight weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to the test article(s) should be recorded as a SAE with details documented in the pregnancy surveillance form. Abortion, whether accidental, therapeutic, or spontaneous should be reported as an SAE.

Male subjects who are not surgically sterile (e.g., vasectomy performed at least six months prior to study entry) and are sexually active with a female partner who is of childbearing

potential[11] must agree to use an effective form of birth control[12] for the duration of the study. Prior to study enrollment, subjects must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

During the study, all subjects should be instructed to contact the investigator immediately if they suspect that their sexual partner might be pregnant (e.g., female sexual partner has missed or late menstrual period).

If the subject suspects that their sexual partner may be pregnant at any time during the study, or if following initiation of study treatment, it is subsequently discovered that a trial subject's sexual partner was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the IRB of any pregnancy associated with the study treatment and keep careful source documentation of the event, including abortion (accidental, therapeutic, or spontaneous) and birth of offspring. Offspring should be followed for a minimum of eight weeks and any congenital anomaly/birth defect in a child born to a subject's sexual partner that was exposed to the test article(s) should be documented.

15. BLINDING/UNBLINDING

Blinding is important for the integrity of this clinical study. However, the blind may be broken in the event of a medical emergency in a subject, in which knowledge of the test article identity is critical to the subject's management. Before breaking the blind for a subject, the investigator should determine that the information is necessary (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not test article related, the problem may be effectively managed by assuming that the subject is receiving active product without the need for unblinding. The need to break the blind should first be discussed with the responsible Medical Monitor and the best method to do this will be determined.

[11] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [at least six months prior to initiation of treatment], or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months in women 50 years of age and older).

[12] Effective forms of birth control include: 1) male condom with spermicide; or 2) use by the female sexual partner of a) hormonal contraceptives [e.g., oral stabilized for at least one full cycle (e.g., four to eight weeks); transdermal, injectable (e.g., Depo-Provera), implantable, or vaginal ring (e.g., NuvaRing) stabilized for at least one week prior to study entry or initiation of sexual relations], b) an IUD for at least one week prior to test article application, or c) a barrier method [e.g., female condom, contraceptive sponge, diaphragm, or cervical cap] with spermicide. Abstinence is also an acceptable method of birth control for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a female partner who is of childbearing potential during the study must agree to use an effective form of birth control for the duration of the study and for 90 days after completion of treatment (if needed).

The test article vials will be color coded with white or yellow labels to maintain the blind. Target Plaque A (LEFT) will receive the test article in the vial with a white label. Target Plaque B (RIGHT) will receive the test article in the vial with a yellow label.

16. CLINICAL SUPPLIES

16.1 Test Article Information

Test articles will be packaged and labeled by PPD Corporation. Detailed information on the packaging/labeling, blinding/unblinding, storage and preparation, dispensing, accountability, etc. is included in CCI

16.2 Supplies Provided by Therapeutics, Inc.

- eCRFs
- Source document draft templates
- Site regulatory binder
- UPT kits
- Triamcinolone cream, 0.1% to treat psoriasis plaques on the CCI (NOTE: subject will be responsible for purchasing OTC hydrocortisone cream or ointment as/if needed and used under the direction of the investigator)
- Bland emollient to treat areas that are not designated Target Plaques
- CCI syringes for test article application
- CCI
- CCI
- CCI digital camera

16.3 Supplies Provided by Investigator

- Personal computer to store and view study images
- Urine collection containers for UPTs, if not provided by the Clinical Lab
- Centrifuge to process blood samples

16.4 Supplies Provided by the Clinical Laboratory

- Supplies to collect and transport urine and blood samples to the clinical laboratory

16.5 Supplies Provided by PPD

- Samples for demonstration to subjects of test article application

17. STATISTICAL CONSIDERATIONS

17.1 Sample Size

This is a pilot, proof of concept study, therefore, no formal sample size calculations were performed for this study.

17.2 Analysis Populations

17.2.1 Safety Population

The Safety population will include all randomized subjects who received and applied test article.

17.2.2 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all randomized subjects who were dispensed the test article.

17.2.3 Per-Protocol Population

The per-protocol (PP) population will include a subset of the ITT population who completed the study without significant protocol deviations (as will be determined prior to unblinding the randomization).

17.3 Endpoints

17.3.1 Efficacy Endpoints

For each endpoint listed below the change from Baseline will be calculated for each treatment at Visits 3, 4, 5, 6, 7, 8, and 9 and summarized. The within subject difference in the change from Baseline scores between DUR-928 and VEH will also be calculated at each visit and summarized as the proportion of subjects in which DUR-928 is better than VEH, DUR-928 is the same as VEH, and DUR-928 is worse than VEH.

1. IGA Score.
2. Clinical Signs of Psoriasis (plaque elevation, scaling, and erythema).
3. LPSI (as a sum of all three parameters including plaque elevation, scaling, and erythema).
4. Target Plaque Area (will only be calculated at Visits 4, 6, and 9).
5. NRS for Pruritus (will only be calculated at Visits 4, 6, and 9).

Treatment success outcomes will also be calculated and summarized as follows for each treatment at Visits 3, 4, 5, 6, 7, 8, and 9.

1. IGA – proportion of subjects with Target Plaques achieving a score of 0 or 1 representing “clear” or “almost clear” with at least 2-grade decrease in severity relative to Baseline.

2. Clinical Signs of Psoriasis – for each clinical sign (plaque elevation, scaling, erythema) the proportion of subjects with Target Plaques achieving a score of 0 or 1 representing "clear" or "almost clear" with at least 2-grade decrease in severity relative to Baseline.
3. NRS for Pruritus – proportion of subjects with Target Plaques that have a Baseline NRS score ≥ 4 and at least a 4 point decrease in NRS score relative to Baseline (will only be calculated at Visits 4, 6, and 9).
4. Target Plaque Area – proportion of subjects with Target Plaques achieving a 50% reduction in Target Plaque Area from Baseline (will only be calculated at Visits 4, 6, and 9).

Additionally, Target Plaque Comparison score results will be summarized at Visits 2, 3, 4, 5, 6, 7, 8, and 9 as the proportion of subjects with each score including, 1A = Target Plaque A is better than Target Plaque B, 0 = Target Plaque A is the same as Target Plaque B, and 1B = Target Plaque A is worse than Target Plaque B.

17.3.2 Safety Endpoints

1. Incidence (severity and causality) of any local and systemic AEs.
2. Number of subjects with presence (and severity) of the following LSRs: burning/stinging, edema, and folliculitis at each time point (except Screening).
3. Changes from Baseline in vital signs at Visit 6/EOT and subsequent visits (if applicable).
4. Changes from Screening in clinical laboratory tests (chemistry, hematology, and urinalysis) at Visit 6/EOT and subsequent visits (if applicable).

17.3.3 Photography

Photography taken at all visits by the sites only shall be used as supportive documentation of efficacy and safety outcomes for this study. An independent photo review may be performed at the discretion of the Sponsor.

17.4 Statistical Methods

All statistical processing will be performed using SAS®. Summary tables (descriptive statistics and/or frequency tables) will be provided for Screening and/or Baseline variables, efficacy variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, median, SD, minimum, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data. Summaries will be provided for each treatment group.

17.4.1 Efficacy Analyses

The efficacy analyses will be conducted on the ITT and PP populations.

For endpoints of change from Baseline, the comparison between DUR-928 and VEH will be conducted using a paired t-test with a significant alpha level of 0.05.

For endpoints of treatment success outcomes, the comparison between DUR-928 and VEH will be conducted using McNemar's test with a significant alpha level of 0.05.

The within subject difference in the change scores and Target Plaque Comparison score between DUR-928 and VEH will also be calculated and summarized descriptively.

17.4.1.1 Dosing Compliance

Descriptive statistics will be used to summarize for each treatment group the duration of treatment (defined as last dose date – first dose date +1), the total number of applications (determined from the doses reported in the Subject Diary), and the percent of expected doses applied for the ITT and PP populations. Subjects who apply at least CCI of the expected total number of applications and have no other evidence of material dosing non-compliance will be considered to be compliant with test article dosing.

17.4.2 Safety Analyses

All safety analyses will be performed on the Safety population.

Safety endpoints will be summarized by descriptive statistics including sample size, mean, SD, median, minimum, and maximum; or by frequency and percentage as appropriate.

Extent of Exposure
Descriptive statistics will be used to summarize the extent of exposure. The total amount of test article used by each subject (prescribed amount of test article multiplied by the number of doses applied) and the mean daily amount of test article applied (total amount of test article applied divided by the duration of treatment) will be calculated.

Physical Examinations
Findings from physical examinations (head and neck, cardiovascular, dermatological, respiratory, gastrointestinal (abdomen), and gross motor and gait) will be recorded in medical history (from assessment at Visit 1/Screening) or as AEs (from assessment at Visit 6/EOT [and subsequent visits, if applicable]).

Vital Signs
Descriptive statistics of vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) at Visit 1/Screening, Visit 2/Baseline, Visit 6/EOT (and subsequent visits, if applicable) will be provided by treatment group.

Clinical Laboratory Tests
Clinical laboratory tests will be evaluated for any material changes during the study period. All laboratory data (hematology, chemistry, and urinalysis) will be listed and reported in

the units received by the laboratory. Shift tables by analyte and by out of range flag will be presented to facilitate the evaluation of change from Visit 1/Screening to Visit 6/EOT (and subsequent visits, if applicable).

Local Skin Reactions
LSRs (burning/stinging, edema, and folliculitis) will be summarized by frequency of each individual LSR for each treatment group.

Adverse Events
All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the test articles, and outcome. Verbatim terms on the eCRFs will be linked to PTs and SOC using the MedDRA mapping system. The PTs and SOC will then be tabulated. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article by treatment group.

Urine Pregnancy Tests
Results from UPTs (if applicable) at Visit 1/Screening, Visit 2/Baseline, and Visit 6/EOT will be provided in a listing.

17.5 Interim Analyses

No interim analyses are planned for this study.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Compliance with Good Clinical Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice guidelines and with other applicable regulations. The investigator and all study staff will conduct the study in compliance with this protocol. The protocol, informed consent documents, recruitment advertisements, and any amendments to these items will have IRB approval prior to study initiation. Voluntary informed consent will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their assigned responsibilities. Contact information for each site and any clinical laboratories used in the study will be maintained up to date in a separate reference document.

18.2 Institutional Review Board and Informed Consent

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to the subject. The investigator should

also provide the IRB with a copy of the product labeling, information to be provided to the subject and any updates. The investigator will submit documentation to the IRB.

The IRB approved consent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The investigator/designee will explain the study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The investigator must provide the subject with a copy of the consent form, in a language the subject understands.

The investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

18.3 Protocol Compliance

The IRB approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

18.4 Protocol Revisions

P must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding this study must be sent to PP

New or altered consent forms required by the IRB due to a protocol change must be signed by all subjects currently enrolled in the study and must be used for any subsequent subject enrollment.

18.5 Study Monitoring

Representatives of P must be allowed to visit all study sites, to review study records, and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff, and to verify that the investigator, study staff, and facilities remain acceptable for the conduct of the study.

Representatives of government regulatory authorities may also evaluate the study records, source documents, investigator, study staff, and facilities.

The investigator should immediately notify P of any audits of this study by any regulatory agency and must promptly provide copies of any audit reports.

18.6 Case Report Form Requirements

This study utilizes eCRFs, validated 21CFR Part 11 compliant electronic data capture (EDC) software will be used to collect data. All requested information must be entered on the eCRFs in the areas provided in a timely manner. When changes or corrections are made in the eCRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change, and the reason for the change. Only individuals who have completed EDC training and are listed on the Delegation of Responsibilities Log with responsibility for eCRF completion will be provided usernames and passwords in order to access the system and make entries on the eCRF.

The investigator or physician sub-investigator must electronically sign and date each subject's eCRF. Individuals who will be providing electronic signatures must first submit documentation with a handwritten signature acknowledging that their electronic signature is a legally binding equivalent to their handwritten signature.

18.7 Reports to Institutional Review Board

The investigator should provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements or Institution procedures.

18.8 Quality Assurance Audits

Representatives from P or a third party selected by P may conduct a quality assurance audit of this study. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authorities, the investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The investigator must notify P in the event of a FDA site audit.

18.9 Records Retention

The investigator must maintain all study records (including test article disposition, informed consents, eCRFs, source documents, correspondence, regulatory documents, contracts, etc.) for the maximum period required by P or the institution where the study is conducted, whichever is longer. Test Article Accountability Logs and original Label Pages (if applicable) must be kept with study records at the site.

The investigator must contact P prior to destroying any records associated with this study.

If the investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to PP

18.10 Record Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject or the subject's parent/guardian (if appropriate), except as necessary for monitoring by PP the FDA or other regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study shall not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from PP must be obtained for the disclosure of any said confidential information to other parties.

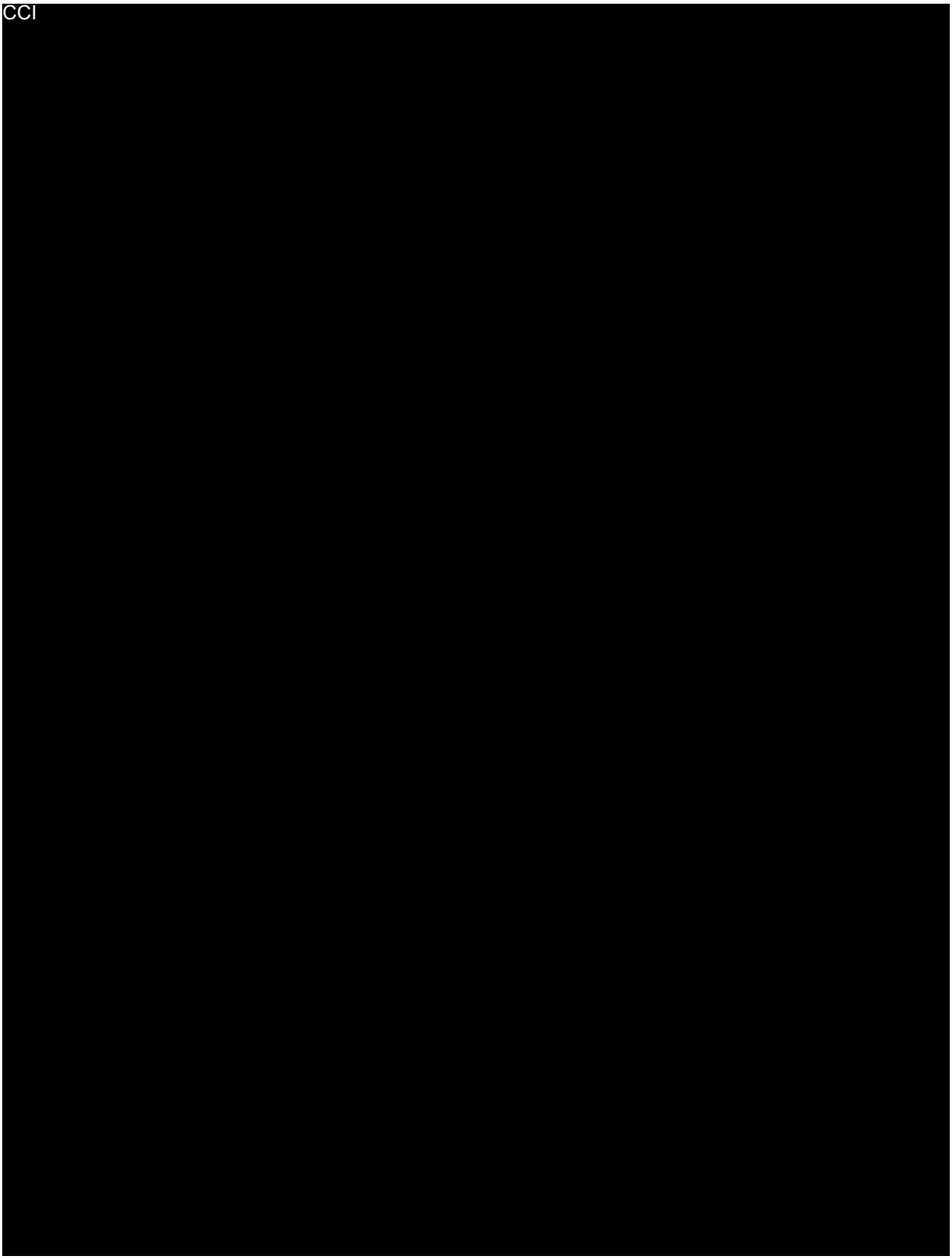
19. REFERENCES

CCI

CCI

[redacted]

CCI



CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

PPD

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI