

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC[®] (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

1.0 TITLE PAGE

Protocol Title: A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC[®] (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

Investigational Product: Tazarotene Cream 0.05%

Population: Approximately 855 males and non-pregnant females, 18 years of age and older, with clinical diagnosis of stable plaque psoriasis

Study Design: A multi-center, double-blind, randomized, vehicle-controlled, parallel-group bioequivalence study with clinical endpoints comparing Tazarotene Cream 0.05% to TAZORAC[®] (tazarotene) Cream 0.05% and both active treatments to a vehicle control in the treatment of stable plaque psoriasis

Sponsor: Fougera Pharmaceuticals Inc.

Protocol Number: 0453-01-01 / NCT02886702

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Protocol Date: 07/26/2016 FINAL
12/20/2016 Rev. 1 FINAL
12/22/2016 Rev. 2 FINAL

Protocol History: 7/26/2016 (Original Protocol)
12/20/2016 (Rev. 1)
12/22/2016 (Rev. 2)



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2.0 KEY STUDY PERSONNEL AND FACILITIES

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CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

3.0 SIGNATURE PAGE

We, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study. The study will be performed according to this protocol, all applicable Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) guidelines and Good Clinical Practice (GCP) standards.



Date



Date



Date



Date



Date

CONFIDENTIAL PROTOCOL

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PRINCIPAL INVESTIGATOR’S SIGNATURE

I agree to conduct protocol 0453-01-01 Rev. 2 in accordance with FDA regulations, ICH guidelines and Good Clinical Practices. I have carefully read and understand the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA), and local regulatory guidelines. I will attempt to complete the study within the time designated. I will ensure that the rights, safety and welfare of subjects under my care are protected. I will ensure control of the drugs under investigation in this study. I will provide copies of the protocol and all other study-related information supplied by the sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information (case report forms, shipment and drug return forms, and all other information collected during the study) and drug disposition in accordance with FDA regulations. I will not enroll any subjects into this protocol until IRB approval and sponsor approval are obtained. I understand that no deviations from the protocol may be made.

Principal Investigator’s Name	
Principal Investigator’s Title	
Principal Investigator’s Email Address	
Site Address	
Site Telephone Number	
Site Fax Number	

Principal Investigator’s Signature

Date

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

4.0 TABLE OF CONTENTS

1.0 TITLE PAGE 1

2.0 KEY STUDY PERSONNEL AND FACILITIES 2

3.0 SIGNATURE PAGE 3

4.0 TABLE OF CONTENTS..... 5

5.0 SYNOPSIS..... 9

6.0 STUDY SCHEMATIC 18

7.0 LIST OF ABBREVIATIONS AND TERMS 19

8.0 INTRODUCTION 20

 8.1 Disease Being Treated 20

 8.2 Availability and Efficacy of Already Approved Therapies 20

 8.3 Scientific and Statistical Considerations 21

 8.4 Justification for use of Placebo 21

 8.5 Risks and Benefits 21

9.0 STUDY OBJECTIVES..... 22

10.0 INVESTIGATIONAL PLAN 22

 10.1 Study Design and Plan Description 22

 10.2 Selection of Study Design..... 23

 10.3 Selection of Study Population..... 24

 10.3.1 Inclusion Criteria..... 24

 10.3.2 Exclusion Criteria 25

 10.3.3 Restrictions During the Study 26

 10.3.4 Withdrawal of Subjects from the Study..... 27

 10.3.5 Early Termination 28

 10.4 Treatments 29

 10.4.1 Treatments Administration 29

 10.4.2 Identity of IP 30

 10.4.3 Study Blind 30

 10.4.4 IP Shipment, Retention and Storage 31

 10.4.5 Method of Assigning Subjects to Treatment Groups 32

 10.4.6 Compliance 33

 10.5 Study Conduct..... 34

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

10.5.1 Visit 1 (Day -14 to Day 1): Screening and Baseline Evaluation..... 34

10.5.2 Visit 2 (Day 28 ± 4 days): Interim Visit..... 35

10.5.3 Visit 3: (Day 56 ± 4 days): Interim Visit 36

10.5.4 Visit 4: (Day 85 ± 4 days) End of Study Visit or Early Termination..... 36

10.6 Study Procedures 37

10.6.1 Informed Consent..... 37

10.6.2 Demographics 37

10.6.3 Medical History..... 37

10.6.4 Pregnancy Test..... 37

10.6.5 Vital Signs..... 37

10.6.6 Concomitant Medication..... 38

10.6.7 Dermatologic Assessment..... 38

10.6.8 IGA 38

10.6.9 PASI..... 38

10.6.10 Application Site Reactions..... 39

10.6.11 Inclusion and Exclusion Criteria Review..... 39

10.6.12 Randomization 39

10.6.13 Dispensing IP 39

10.6.14 Returning IP 39

10.6.15 Subject Dosing Instructions and Diary 40

10.6.16 Standardized Sunscreen 40

10.6.17 Health Status/AEs 40

10.7 AEs/SAEs 40

10.7.1 Definitions..... 41

10.7.2 Severity of AEs 42


10.7.3 Relationship to the IP..... 42

10.7.4 AE Documentation..... 42

10.7.5 SAE Reporting..... 43

10.7.6 Pregnancies 46

10.7.7 Quality Complaints 46

 46

10.7.9 Reconciliation 47

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

11.0 STATISTICAL METHODS 47

 11.1 Statistical Plan..... 47

 11.2 Sample Size Determination..... 48

 11.3 Study Populations 48

 11.3.1 PP Population..... 48

 11.3.2 Modified Intent-to-Treat (mITT) Population 49

 11.3.3 Safety Populations..... 49

 11.4 Baseline Comparability..... 49

 11.5 Efficacy Endpoints..... 50

 11.6 Primary and Secondary Endpoint Analyses..... 50

 11.7 Treatment-by-Site Interaction and Pooling of Clinical Sites 51

 11.8 Safety Analysis 51

12.0 REGULATORY OBLIGATIONS..... 51

 12.1 Institutional Review Board 51

 12.2 Subject Confidentiality 52

 12.3 Study Documentation..... 52

 12.3.1 Protocol..... 52

 12.3.2 Informed Consent..... 53

 12.3.3 Protocol and Informed Consent Changes..... 53

 12.3.4 Source Documents and Case Report Forms..... 53

 12.3.5 Drug Accountability..... 54

 12.3.6 Drug Storage 54

 12.3.7 Retention of Reserve Samples 54

 12.3.8 Return of Clinical Supplies..... 55

 12.3.9 Pregnancy and Breastfeeding..... 55

 12.3.10 Reporting Safety Information to the IRB..... 56

 12.3.11 Record Retention..... 56

 12.3.12 Study Monitoring and Auditing..... 57

 12.3.13 Confidentiality, Use of Information and Publication..... 60


 12.3.14 End of the Trial 60

 12.3.15 Clinical Study Report..... 61

 12.3.16 Termination of the Study 61

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

	62
14.0 APPENDICES	63
14.1 APPENDIX A: Investigator’s Global Assessment of Disease Severity	63
14.2 APPENDIX B: Psoriasis Area Severity Index at the Target Lesion Site	64
14.3 APPENDIX C: Application Site Reactions	65
14.4 APPENDIX D: TAZORAC® (tazarotene) Product Insert	66
14.5 APPENDIX E: Amendments to the Protocol	67

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

5.0 SYNOPSIS

Protocol Number	0453-01-01
Title	A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (Tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis
Objectives	<ol style="list-style-type: none">1. Evaluate the therapeutic equivalence of the Test product, Tazarotene Cream 0.05% (Fougera Pharmaceuticals Inc.) to the Reference product, TAZORAC® (tazarotene) Cream 0.05% (Allergan, Inc.) in the treatment of stable plaque psoriasis.2. Demonstrate the superiority of the efficacy of the Test and Reference (active) products over that of the Placebo in the treatment of stable plaque psoriasis.3. Compare the safety of the Test, Reference and Placebo products in the treatment of stable plaque psoriasis.
Sponsor	Fougera Pharmaceuticals Inc.
Investigational Products	<ul style="list-style-type: none">• Test: Tazarotene Cream 0.05% (Fougera Pharmaceuticals Inc.)• Reference: TAZORAC® (tazarotene) Cream, 0.05% (Allergan, Inc.)• Placebo: Placebo (vehicle) Cream (Fougera Pharmaceuticals Inc.)
Dose and Route of Administration	Subjects will be instructed to apply the investigational product (IP) topically, once daily, in the evening, for 84 days ± 4 days (12 weeks). Enough cream should be applied (2 mg/cm ²) to cover only the lesions with a thin film. Hands should be washed thoroughly before and after each application. It is recommended that if a bath or shower is taken before application, the skin should be dry before applying the cream.
Treatment Period	84 days (12 weeks) ± 4 days
Treatment Randomization	1: 1: 1 (Test: Reference: Placebo)
Subject Populations	<p>Approximately 855 male and non-pregnant female subjects, at least 18 years of age who meet all of the inclusion criteria and none of the exclusion criteria, will be enrolled in order to obtain [REDACTED] subject in the modified Intent-to-Treat (mITT) population and [REDACTED] subjects in the per-protocol (PP) population.</p> <p>The primary inclusion criteria are:</p> <ul style="list-style-type: none">• Clinical diagnosis of stable (at least 6 months) plaque psoriasis involving at least 2% and no more than 20% of Body Surface Area (BSA) not including the scalp and intertriginous areas

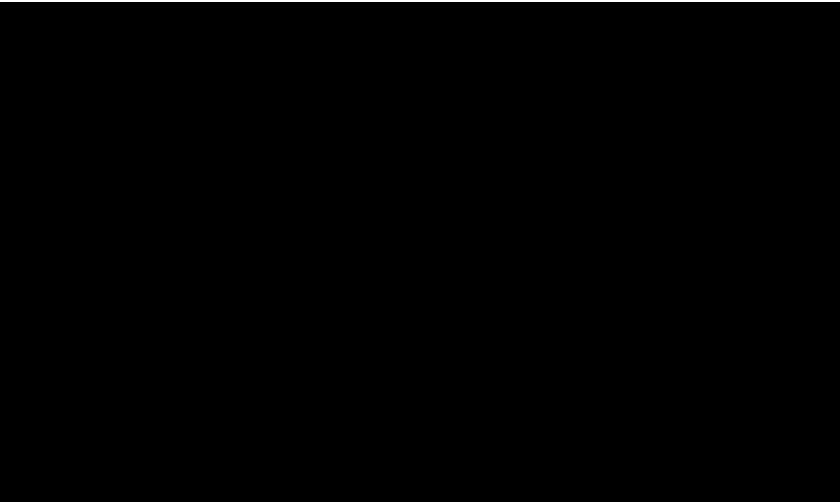
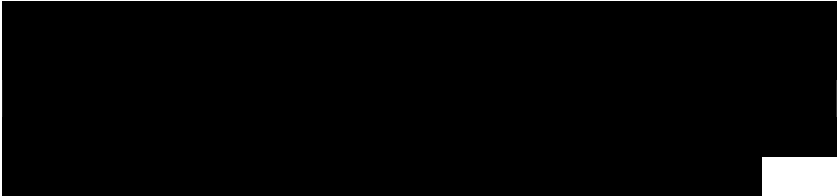
CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

	<ul style="list-style-type: none"> • An Investigator's Global Assessment (IGA) of disease severity of at least moderate severity (Score ≥ 3) as an overall assessment of lesions to be treated • A minimum plaque elevation of at least moderate severity (Score ≥ 3) at the target lesion (the most severe lesion at Baseline) 				
Study Design	A multi-center, double-blind, randomized, vehicle-controlled, parallel-group bioequivalence study with clinical endpoints comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream, 0.05% and both active treatments to a vehicle control in the treatment of stable plaque psoriasis.				
Investigative Sites	Approximately 30 sites in the United States				
Study Conduct	<p>Eligible subjects will be randomized in a 1:1:1 ratio to one of the three treatment groups (Test, Reference or Placebo) at Visit 1. IP will be dispensed at Visit 1. Subjects will be instructed to apply enough cream (2 mg/cm²) to cover only the psoriatic lesions with a thin film. The first dose will be applied on the evening of Day 1. The subject will then continue to apply a thin film (2 mg/cm²) of the product once daily, in the evening, to cover only psoriatic lesions until the evening before Visit 4 (Day 85 \pm 4 days). Subjects will attend the following scheduled clinic visits:</p> <ul style="list-style-type: none"> • Visit 1 - Screening/Baseline: Day -14 to 1 • Visit 2 - Interim Visit: Day 28 \pm 4 days • Visit 3 - Interim Visit: Day 56 \pm 4 days • Visit 4 - End of Study/Early Termination: Day 85 \pm 4 days <p>Efficacy evaluations will be based on dermatological assessments performed in the clinic. The primary endpoint is the proportion of subjects with treatment success on the IGA at the Week 12 visit (Day 85 \pm 4, End of Study). See Appendix A for IGA scale.</p>				
Inclusion Criteria	<ol style="list-style-type: none"> 1. Male or non-pregnant, non-lactating female, ≥ 18 years of age with a clinical diagnosis of stable (at least 6 months) plaque psoriasis. 2. [REDACTED] 3. Females of childbearing potential must not be lactating or pregnant at Visit 1 (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin) and [REDACTED] <table border="1" data-bbox="522 1732 1372 1822"> <tr> <td data-bbox="522 1732 945 1780">Childbearing Potential</td> <td data-bbox="945 1732 1372 1780">Non-Childbearing Potential</td> </tr> <tr> <td data-bbox="522 1780 945 1822">Defined as:</td> <td data-bbox="945 1780 1372 1822">Defined as:</td> </tr> </table>	Childbearing Potential	Non-Childbearing Potential	Defined as:	Defined as:
Childbearing Potential	Non-Childbearing Potential				
Defined as:	Defined as:				



CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

	<p>Evidence of menses in the past 12 months</p>	<p>Post-menopausal, defined as women who have been amenorrheic for at least 12 consecutive months, without other known or suspected primary cause.</p>
<p>Amenorrhea for ≥ 12 months, but the amenorrhea is possibly due to other causes, including prior chemotherapy, anti-estrogens or ovarian suppression</p>	<p>Sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy, or bilateral oophorectomy) with surgery at least 4 weeks before Screening. Tubal ligation will not be considered a surgically sterile method.</p>	
	<p>4. </p> <p>5. Have clinical diagnosis of stable (at least 6 months) plaque psoriasis involving at least 2% and no more than 20% BSA not including the scalp and intertriginous areas.</p> <p>6. Have an IGA of disease severity grade of at least moderate severity (score ≥ 3 per Appendix A).</p> <p>7. Have a Psoriasis Area Severity Index (PASI) minimum plaque elevation grade of at least moderate severity (score ≥ 3 per Appendix B) at the target lesion site. The most severe lesion at Baseline should be identified as the target lesion.</p> <p>8. </p>	



CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

	<p>9. Willing to avoid constant sun exposure and the use of tanning booths or other ultraviolet light sources during their participation in the study.</p> <p>10. </p>
<p>Exclusion Criteria</p>	<ol style="list-style-type: none">1. Females who are pregnant, breast feeding, planning a pregnancy or do not agree to use an acceptable form of birth control throughout the study.2. Has a current diagnosis of unstable forms of psoriasis in the treatment area including guttate, erythrodermic, exfoliative or pustular psoriasis.3. Has clinically infected psoriasis at Baseline.4. In the Investigators opinion, subject has other inflammatory skin disease in the treatment area that may confound the evaluation of the plaque psoriasis (i.e., atopic dermatitis, contact dermatitis, eczema, tinea corporis).5. Has presence of pigmentation, extensive scarring, pigmented lesions or sunburn in the treatment area which could interfere with the rating of efficacy parameters.6. Has a history of psoriasis unresponsive to topical treatments and/or biologic treatments.7. Has a history of hypersensitivity or allergy to tazarotene, retinoids, and/or any component of the IP (Test, Reference or Placebo). Please refer to the Reference Listed Drug Package Insert for the components of the IP8. Current signs or symptoms of immunosuppression.9. 10. Has treated with any marketed or investigational biologics for psoriasis (i.e., infliximab, adalimumab, alefacept, etc.) within 6 months before Baseline.11. Has been treated with chemotherapy or radiation therapy within 3 months before Baseline.12. Has treated with any immunosuppressive drugs (i.e., tacrolimus, pimecrolimus) or oral retinoids within 2 months before Baseline.13. Has treated with systemic steroids, systemic antibiotics, systemic anti-psoriatic treatment (i.e., methotrexate, cyclosporine, hydroxyurea),

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

	<p>PUVA therapy, ultraviolet-B Therapy or systemic anti-inflammatory agents within 1 month before Baseline. </p>  <p>14. Has treated with topical anti-psoriatic drugs (i.e., salicylic acid, anthralin, coal tar, calcipotriene, tazarotene), topical corticosteroids or topical retinoids within 2 weeks before Baseline.</p> <p>15. Inability to understand the protocol requirements, instructions and study-related restrictions, the nature, scope and possible consequences of the clinical study.</p> <p>16. Receipt of any drug and/or IP as part of a research study within the 30 days before Baseline.</p> <p>17. Subjects who consume excessive amounts of alcohol, abuse drugs, or have any social condition that would, in the Investigator’s opinion, compromise compliance with this protocol.</p> <p>18. Previous participation in this study.</p> <p>19. Employees of the Investigator or research center or their immediate family members.</p>
<p>Efficacy Endpoints</p>	<p><u>Primary Efficacy Endpoint</u></p> <p>Proportion of subjects with treatment success (defined as none, minimal or mild disease, a score of 0, 1 or 2 within the treatment area) on the IGA at the Week 12 visit (Day 85 ± 4, End of Study).</p> <p><u>Secondary Efficacy Endpoints</u></p> <ol style="list-style-type: none">1. Proportion of subjects with disease severity at the Week 12 visit (Day 85 ± 4, End of Study) consistent with none or minimal, a score of 0 or 1, within the treatment area on the IGA, and2. Proportion of subjects with target site plaque elevation, scaling and erythema scores of less than or equal to 1 on the PASI at the Week 12 visit (Day 85 ± 4, End of Study).

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

Measures	The following scales will be used for evaluation of Baseline disease severity and treatment effect.			
	IGA of Disease Severity			
	Score	Grade	Definition	
	0	None	No plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale: no erythema	
	1	Minimal	Essentially flat with possible trace elevation; faint erythema; no psoriatic scale	
	2	Mild	Slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered	
	3	Moderate	Moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarse scales with most lesions partially covered	
	4	Severe	Marked elevation with hard, sharp edges to plaque; severe erythema (very red coloration); coarse, thick scales with virtually all lesions covered and a rough surface	
	5	Very Severe	Very marked elevation with very hard, sharp edges to plaque; very severe erythema (extreme red coloration); very coarse, thick scales with all lesions covered and a very rough surface	
	Subjects with IGA grade of ≥ 3 will be enrolled in the study			
PASI at the Target Lesion Site				
Score	Grade	Erythema	Scaling	Plaque Elevation
0	Clear	No evidence of erythema	No evidence of scaling	No evidence of plaques above normal skin level
1	Almost Clear	Pink discoloration, minimal erythema	Occasional fine scales hardly noticeable	Slight, just discernible elevation above normal skin level
2	Mild	Light red coloration	Slight but definite roughness, fine	Discernible elevation above normal

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

				scale present, no cracking	skin level upon examination, but not pronounced
	3	Moderate	Moderate redness, but not dark	Moderate roughness, somewhat coarse scaling	Definite plaque formation with rounded/sloped edges to plaque
	4	Severe	Dark red coloration	Marked roughness, coarse/thick scaling, cracking may be evident	Marked elevation with hard, distinct edges to plaque
	5	Very Severe	Very dark red coloration with induration present	Very thick scales covering extensive area severe cracking/fissures may be evident	Very marked elevation, very hard and sharp edges to plaque
Evaluation of Therapeutic Equivalence and Superiority	<p>The primary analyses for evaluating the therapeutic equivalence of the Test and Reference treatments, and the superiority of each active treatment over the Placebo, will be based on the proportion of subjects with treatment success (defined as "none, minimal or mild disease, a score of 0, 1 or 2, within the treatment area") on the IGA at Week 12 visit (Day 85 ± 4, End of Study).</p> <p>The statistical analyses for equivalence for binary outcomes for the primary and two secondary endpoints will be based on a Yates' continuity-corrected confidence interval on the Test minus Reference difference (T-R) in proportions. Superiority will be tested at the 5% significance level using a Cochran-Mantel-Haenszel exact test stratified by clinical site for Test versus Placebo and Reference versus Placebo for the three endpoints.</p> <p><u>Therapeutic Equivalence Analysis</u></p> <p>Therapeutic equivalence will be evaluated for both primary and secondary endpoints using the PP population, with results in the mITT population being supportive. For the dichotomized primary endpoint (proportion of treatment success), if the 90% confidence interval (with Yates' Correction Factor) of the difference between the proportion of subjects considered a "treatment success" in the Test and the Reference treatment groups at Week 12, compared to Baseline, is contained within the pre-defined equivalence</p>				

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

	<p>limits [-20%, +20%], then therapeutic equivalence will be considered to have been supported for the endpoint. The same statistical approach will be conducted for analysis of the two dichotomized secondary endpoints in the PP and mITT populations.</p> <p>To declare therapeutic equivalence of the Test product to the Reference product, therapeutic equivalence must be demonstrated for only the primary endpoint in the PP population.</p> <p><u>Superiority to Placebo Analysis</u></p> <p>The primary measure of superiority will be evaluated using the mITT population and last observation carried forward (LOCF) for missing efficacy values. The results in the PP population will be considered supportive. The superiority of the Test and Reference products over Placebo will be concluded for the primary endpoint if the proportion of treatment success at Week 12 is statistically superior to Placebo ($p < 0.05$, two-sided) using the mITT population and LOCF. The same statistical approach will be conducted for analysis of the two dichotomized secondary endpoints in the mITT and PP populations.</p> <p>To declare superiority of the Test and Reference products over Placebo, their superiority must be demonstrated for only the primary endpoint in the mITT population.</p>
Safety Analysis	<p>Adverse events (AEs) will be classified using standard MedDRA terminology Version 18.1 or higher and summarized by treatment group. Summary tables comparing the type, date of onset, date of resolution, incidence, severity, relationship to the IP, outcome and action taken will be prepared by treatment group. Should sufficient data exist, AE frequencies will be compared among treatments using Fisher's exact test or a similar test. Application site reactions (erythema, dryness, burning/stinging, erosion, edema, pain, itching) recorded at each visit will be compared among treatment groups. A descriptive analysis comparing the application site reactions for each treatment group will be created.</p> <p>Concomitant medication use during the treatment period will be tabulated by subject.</p> <p>Signs and symptoms of psoriasis will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/subject considers that it is in the subject's best interest to be dropped from continued participation in the study and given alternative therapy for their condition.</p> <p>All randomized subjects who received IP will be included in the comparative safety analysis.</p>
Sample Size Determination	<p>Sample size calculations were performed using [REDACTED]</p> <p>For the primary endpoint analysis, the rate of treatment success for the</p>

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

Reference treatment after 12 weeks of treatment is expected to be approximately [REDACTED] in the PP population. Assuming that the rates of treatment success for Test and Reference treatments are the same, a sample size of [REDACTED] subjects in each active group in the PP population will provide approximately [REDACTED] power to demonstrate therapeutic equivalence (i.e., the 90% confidence interval (Yates' continuity-corrected) of the absolute difference between the Test and Reference rates of treatment success is within a defined equivalence range [-20% to + 20%]).

The rates of treatment success for the Placebo and active treatment groups after 12 weeks of treatment are assumed to be approximately [REDACTED] and at least [REDACTED] respectively, in the mITT population. Using a 1:1 (active: placebo) randomization scheme, and assuming the conversion rate from mITT to PP population will be about [REDACTED] [REDACTED] subjects in each treatment group (Test, Reference and Placebo) of the mITT population will provide at least [REDACTED] power to demonstrate superiority of active over Placebo at the [REDACTED] significance level ($p < 0.05$, two-sided continuity-corrected Z-Tests and a pooled response rate for the standard error of the difference in proportions).

Under the above assumptions, the overall study power to demonstrate therapeutic equivalence and superiority is estimated to be at least [REDACTED]. To allow for approximately [REDACTED] of subjects who may drop out from the study or are otherwise non-evaluable, up to 855 subjects may be randomized to obtain [REDACTED] subjects in the mITT population (i.e., [REDACTED] per treatment arm).

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

6.0 STUDY SCHEMATIC

PROCEDURE	VISIT 1 (Day -14 to 1) Screening/ Baseline	VISIT 2 (Day 28 ± 4 Days) Interim Visit	VISIT 3 (Day 56 ± 4 Days) Interim Visit	VISIT 4 (Day 85 ± 4 Days)* End of Study/ Early Termination
Informed Consent	X [†]			
Medical History/ Demographics	X [†]			
Pregnancy Test [†]	X [†]	X	X	X
Vital Signs	X [†]			X
Dermatologic Assessment	X [†]			
IGA	X [†]	X	X	X
PASI Assessment	X [†]	X	X	X
Application Site Reactions	X	X	X	X
Inclusion/Exclusion Criteria Review	X [†]			
Concomitant Medication	X [†]	X	X	X
Randomization	X			
Dispense IP	X	X ^{**}	X ^{**}	
Return of IP		X ^{**}	X ^{**}	X
Dispense Subject Diary/Supplies	X	X	X	
Collect/Review Subject Diary		X	X	X
Adverse Events		X	X	X
Discharge from Study				X

* Dosing regimen is once daily in the evening for 84 days (Day 1 to Day 84) through the evening before Visit 4 (Day 85 ± 4)

** If applicable, based on use of previously dispensed product.

† For females of childbearing potential

‡ Procedures performed as part of the screening assessment, before randomization

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A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

7.0 LIST OF ABBREVIATIONS AND TERMS

AE	Adverse Event
ADR	Adverse Drug Reaction
ADaM	Analysis Dataset Model
ANOVA	Analysis of Variance
BSA	Body Surface Area
C	Celsius
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Consortium
CFR	Code of Federal Regulations
CI	Confidence Interval
cm	Centimeter
CRO	Clinical Research Organization
eCRF	electronic Case Report Form
eCTD	electronic Common Technical Document
F	Fahrenheit
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
LOCF	Last Observation Carried Forward
LPPV	Local Person for Pharmacovigilance
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	modified Intent-to-Treat
ml	milliliter
NDA	New Drug Application
OGD	Office of Generic Drugs
OHRP	Office of Human Rights Protection
OTC	Over-The-Counter
PASI	Psoriasis Area Severity Index
PD	Protocol Deviation
PP	Per-Protocol
RLD	Reference Listed Drug
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Model

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

8.0 INTRODUCTION

8.1 Disease Being Treated

Psoriasis is an immune (T-cell)-mediated inflammatory skin disease that affects approximately 2% of the western population.¹ The most common type of psoriasis is plaque psoriasis, which is characterized by the presence of raised, thickened red lesions that are covered by silvery white scales, most commonly seen on the knees and/or elbows. Although there are reports implicating a genetic association with the disease, there are also studies that have established a set of psoriasis triggers including stress, medications (such as lithium, antimalarials, indomethacin, quinidine and beta blockers), injury or infection. The condition is considered chronic although the frequency and severity of outbreak in an individual can fluctuate without apparent cause.¹⁻³

Treatment of plaque psoriasis depends on the severity of the condition, previous treatment regimens and personal preference of the subject. For mild to moderate plaque psoriasis, topical treatments and phototherapy are the preferred treatment modalities. For more severe cases, oral or injectable systemic therapy may be warranted; however, the side effect profiles of these products limit their use.

Psoriasis is typically described as mild, moderate or severe and by assessing the percentage of body surface area (BSA) affected and covered by psoriasis lesions. Several scale systems have been developed and many are in use in the clinical setting; however, a severity scale, despite being a convenient scoring system, does not capture the true burden of psoriasis for many patients. Psoriasis is associated with a broad range of medical and psychosocial comorbidities that erode quality of life of the patients. Subjects selected for this study suffer from plaque psoriasis of at least moderate severity and an IGA of 3 or more.

8.2 Availability and Efficacy of Already Approved Therapies

Treatment of plaque psoriasis depends on the severity of the condition, previous treatment regimens and personal preference of the subject. Psoriasis treatments historically include topical creams, sprays, lotions and foams. Examples of marketed products include corticosteroids (Topicort®, Clobex™), Vitamin A & D derivatives (Tazorac®, Dovonex®), NSAIDs (salicylic acid), etc. For more severe cases, systemic therapy (methotrexate, oral retinoids, UV light, biologics, etc.) may be warranted; however, the side effect profiles of these products limit their use.^{1,2,4-6}

Tazarotene is one of a class of drugs known as the acetylenic retinoids. Psoriasis is a chronic immune-mediated disease that is characterized by the hyperproliferation and abnormal differentiation of keratinocytes and by inflammation. The epidermal changes associated with psoriasis may be due to the infiltration of inflammatory T lymphocytes and the release of cytokines in response to antigenic stimulation. Tazarotene is a retinoic acid receptor-specific retinoid with demonstrated efficacy in the topical treatment of psoriasis. Tazarotene down-regulates markers of keratinocyte differentiation, keratinocyte proliferation and inflammation. The drug also up-regulates three novel genes TIG-1 (tazarotene-induced gene-1), TIG-2 and TIG-3, which may mediate an antiproliferative effect. The effect of tazarotene on these markers is probably a direct effect on gene expression rather than an indirect effect associated with disease improvement.

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

8.3 Scientific and Statistical Considerations

Tazarotene has low systemic absorption and rapid elimination from semi-solid topical formulations of TAZORAC®. In a multiple-dose study with a once daily dose of tazarotene cream, 0.1% administered for 14 consecutive days to nine psoriatic subjects, mean peak plasma concentrations of 2.31 ng/mL occurring 8 hours after the final dose were observed for the active metabolite of tazarotene (tazarotenic acid).⁷ The 21 Code of Federal Regulations Sections 320.24 (Revised April 1, 2014) requires that in-vivo pharmacokinetic testing in humans is the preferred method in evaluating therapeutic equivalence. However, circumstances for which measurement of the active moieties in biological fluids is not possible or provides low concentrations, a pharmacodynamic response study indicative of clinical safety and efficacy can be considered.⁸⁻¹⁰ Based on the low systemic bioavailability of tazarotene from the topical cream product, a comparative clinical efficacy study is considered the most appropriate method to evaluate the therapeutic equivalence of two tazarotene topical cream, 0.05% formulations.



8.4 Justification for use of Placebo

A Placebo group is included to confirm the sensitivity of the study and minimize the possibility of a false positive result of therapeutic equivalence. Therefore, in addition to demonstrating therapeutic equivalence between Test and Reference products, both active products must show statistical superiority to the Placebo.^{11,12}

Eligible subjects will have a 33.33% chance of being randomized to Placebo (1:1:1 randomization scheme of Test: Reference: Placebo).



8.5 Risks and Benefits

The risks and benefits to subjects enrolled in clinical research studies that include a Placebo treatment group must be carefully considered based on three main criteria, namely: the disease being treated, the availability, efficacy and safety of approved therapies, and the scientific and statistical requirements of the desired outcome of the research study. The Office of Human Rights Protection (OHRP), a Division of the United States Federal Government's Department of Health

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC[®] (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

and Human Services, has issued a detailed guidebook to IRBs that includes discussion on the use of placebos in clinical studies.¹³

Randomized subjects will be enrolled in the study for 85 ± 4 days. Although the potential for any drug-related side effects of significance occurring during the study is low, the risk is higher in the two active treatment groups than in the Placebo group. Topical application of Tazarotene can lead to drug-related effects, mainly affecting the application sites: skin itching, irritation, dryness and burning or pain sensation represent the most common side effects.

All subjects enrolled in this study will receive Investigator evaluation of their condition over 85 days. In addition, the subject will be paid for their participation, and any payments will be reviewed by the IRB and disclosed to the subject, via the informed consent form (ICF).

9.0 STUDY OBJECTIVES

The objectives of this study are to:

1. Evaluate the therapeutic equivalence of the Test product, Tazarotene Cream 0.05% (Fougera Pharmaceuticals Inc.) to the Reference product, TAZORAC[®] (tazarotene) Cream, 0.05% (Allergan) in the treatment of stable plaque psoriasis.
2. Demonstrate the superiority of the efficacy of the Test and Reference (active) products over that of Placebo in the treatment of stable plaque psoriasis.
3. Compare the safety of the Test, Reference and Placebo products in the treatment of stable plaque psoriasis.

10.0 INVESTIGATIONAL PLAN

10.1 Study Design and Plan Description

This multi-center, double-blind, randomized, vehicle-controlled, parallel-group, bioequivalence clinical study has been designed to evaluate the efficacy and safety of a generic tazarotene cream 0.05% (Fougera Pharmaceuticals Inc.) compared to the FDA Reference Listed Drug (RLD) TAZORAC[®] (tazarotene) Cream 0.05% (Allergan) in subjects with a clinical diagnosis of stable plaque psoriasis of at least moderate severity. Additionally, both the Test product and Reference (i.e., the RLD) products will be tested for superiority to a Placebo. Subjects with confirmed stable plaque psoriasis will apply the investigational product (IP) once daily, in the evening, to psoriatic lesions for 84 ± 4 days (12 weeks).

Before any study-specific procedures are performed, all subjects will read and sign the IRB-approved ICF.

Each site will develop an individualized recruitment plan to collectively enroll approximately 855 eligible subjects, 18 years of age and older, with a clinical diagnosis of stable plaque psoriasis and meeting the inclusion/exclusion criteria. Subjects will be randomized to one of the three IPs as follows:

- **Test:** Tazarotene Cream, 0.05% (Fougera Pharmaceuticals Inc.)
- **Reference:** TAZORAC[®] (tazarotene) Cream, 0.05% (Allergan, Inc.)
- **Placebo:** Placebo (vehicle) Cream (Fougera Pharmaceuticals Inc.)

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

Subjects will attend the following scheduled clinic visits:

- Visit 1 - Screening/Baseline: Day -14 to Day 1
- Visit 2 - Interim Visit: Day 28 ± 4 days
- Visit 3 - Interim Visit: Day 56 ± 4 days
- Visit 4 - End of Study/Early Termination: Day 85 ± 4 days

At Visit 1, eligible subjects will be randomized to the Test, Reference or Placebo product in a 1:1:1 ratio using the [REDACTED] system, which is an interactive response technology (IRT) system provided by the IRT provider. Study subjects will be provided with [REDACTED] of IP. [REDACTED] may be dispensed to the subject at the discretion of the Investigator if the subject has a high BSA affected with plaque psoriasis at the time of dispensation that would warrant additional product. At Visit 2 and Visit 3, subjects who continue to be eligible for continuation in the study can be dispensed [REDACTED], as needed based on the subject's current BSA affected and the amount of IP remaining from the tube(s) previously dispensed. Further, any empty tubes will be collected at these visits. At Visit 4, all tubes will be collected (used and unused). A subject may return for an Unscheduled Visit at any time, should they require a resupply of IP (i.e., tube lost; all IP used between visits). It is estimated that approximately [REDACTED] tubes, but up to [REDACTED] tubes may be needed to dose a subject with high BSA involvement (~20% BSA) for the treatment period (depending upon their treatment response over the 12 weeks). Subjects with less BSA involvement will need significantly less IP (approximately [REDACTED] to [REDACTED] tubes).

The day that the subject administers their first dose of IP will be considered Day 1. [REDACTED]

[REDACTED] For all other subjects, the first dose (Day 1) of IP will be applied on the evening of Visit 1.

The subject will be instructed to apply enough cream (2 mg/cm²) to cover only the psoriatic lesions with a thin film (2 mg/cm²) once daily, in the evening, until the evening before Visit 4 (Day 85 ± 4 days). There will be no application of the product on the day of the End of Study visit.

Efficacy evaluations will be based on dermatological assessments in the clinic. The primary statistical analysis of interest is the (1) proportion of subjects with treatment success (defined as none, minimal or mild disease, a score of 0, 1 or 2, within the treatment area) on the Investigator's Global Assessment (IGA) at the Week 12 visit. The secondary analyses are (1) proportion of subjects with disease severity at the Week 12 visit consistent with none or minimal, a score of 0 or 1, within the treatment area on the IGA, and (2) proportion of subjects with target site plaque elevation, scaling, and erythema scores of less than or equal to one on the PASI at the Week 12 visit.

10.2 Selection of Study Design

This protocol is designed based on studies conducted as a part of the NDA (21-184) for TAZORAC® Cream, 0.05% and the FDA draft guidance for tazarotene cream 0.05%, released in April, 2011.¹⁴

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

Statistical analyses of the clinical data will be based on recommendations in the FDA guidance or communications with the Office of Generic Drugs (OGD)/FDA.^{9,15}

10.3 Selection of Study Population

10.3.1 Inclusion Criteria

1. Male or non-pregnant, non-lactating female, ≥ 18 years of age with a clinical diagnosis of stable (at least 6 months) plaque psoriasis.

2.

3. Females of childbearing potential must not be lactating or pregnant at Visit 1 (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin) and

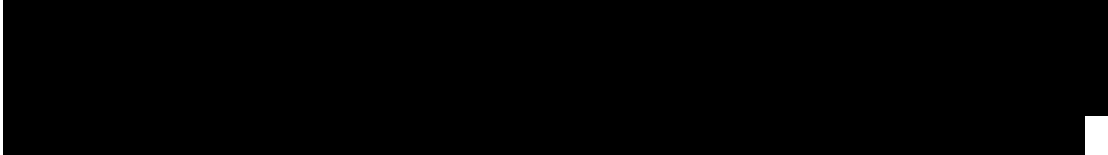
Childbearing Potential Defined as:	Non-Childbearing Potential Defined as:
Evidence of menses in the past 12 months	Post-menopausal, defined as women who have been amenorrheic for at least 12 consecutive months, without other known or suspected primary cause.
Amenorrhea for ≥ 12 months, but the amenorrhea is possibly due to other causes, including prior chemotherapy, anti-estrogens or ovarian suppression	Sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy, or bilateral oophorectomy) with surgery at least 4 weeks before Screening. Tubal ligation will not be considered a surgically sterile method.

4.

5. Have clinical diagnosis of stable (at least 6 months) plaque psoriasis involving at least 2% and no more than 20% BSA not including the scalp and intertriginous areas.

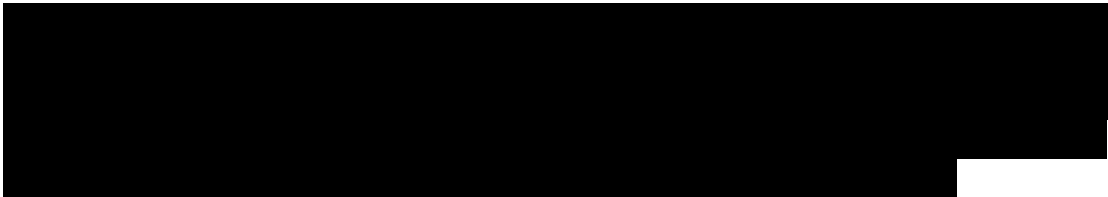
CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

6. Have an IGA of disease severity grade of at least moderate severity (score ≥ 3 per Appendix A).
7. Have a Psoriasis Area Severity Index (PASI) minimum plaque elevation grade of at least moderate severity (score ≥ 3 per Appendix B) at the target lesion site. The most severe lesion at Baseline should be identified as the target lesion.
8. 
9. Willing to avoid constant sun exposure and the use of tanning booths or other ultraviolet light sources during their participation in the study.

10. 

10.3.2 Exclusion Criteria

1. Females who are pregnant, breast feeding, planning a pregnancy or do not agree to use an acceptable form of birth control throughout the study.
2. Has a current diagnosis of unstable forms of psoriasis in the treatment area including guttate, erythrodermic, exfoliative or pustular psoriasis.
3. Has clinically infected psoriasis at Baseline.
4. In the Investigators opinion, subject has other inflammatory skin disease in the treatment area that may confound the evaluation of the plaque psoriasis (i.e., atopic dermatitis, contact dermatitis, eczema, tinea corporis).
5. Has presence of pigmentation, extensive scarring, pigmented lesions or sunburn in the treatment area which could interfere with the rating of efficacy parameters.
6. Has a history of psoriasis unresponsive to topical treatments and/or biologic treatments.
7. Has a history of hypersensitivity or allergy to tazarotene, retinoids, and/or any component of the IP (Test, Reference or Placebo). Please refer to the RLD Package Insert for the components of the IP.
8. Current signs or symptoms of immunosuppression.
9. 
10. Has treated with any marketed or investigational biologics for psoriasis (i.e., infliximab, adalimumab, alefacept, etc.) within 6 months before Baseline.

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

11. Has been treated with chemotherapy or radiation therapy within 3 months before Baseline.
12. Has treated with any immunosuppressive drugs (i.e., tacrolimus, pimecrolimus) or oral retinoids within 2 months before Baseline.
13. Has treated with systemic steroids, systemic antibiotics, systemic anti-psoriatic treatment (i.e., methotrexate, cyclosporine, hydroxyurea), PUVA therapy, ultraviolet-B Therapy or systemic anti-inflammatory agents within 1 month before Baseline. [REDACTED]
14. Has treated with topical anti-psoriatic drugs (i.e., salicylic acid, anthralin, coal tar, calcipotriene, tazarotene), topical corticosteroids or topical retinoids within 2 weeks before Baseline.
15. Inability to understand the protocol requirements, instructions and study-related restrictions, the nature, scope and possible consequences of the clinical study.
16. Receipt of any drug and/or IP as part of a research study within the 30 days before Baseline.
17. Subjects who consume excessive amounts of alcohol, abuse drugs, or have any social condition that would compromise compliance, in the Investigator's opinion, with this protocol.
18. Previous participation in this study.
19. Employees of the Investigator or research center or their immediate family members.


10.3.3 Restrictions During the Study

The following concomitant medications, products or procedures will not be allowed while enrolled in the study.

- Use of the following topical products on or near the treatment area:
 - Moisturizers
 - New brands of Make-up
 - Creams, ointments, lotions, powders
 - Topical Corticosteroids
- Topical or systemic anti-psoriatic treatments (e.g., anthralin, coal tar, tazarotene, retinoids, tacalcitol, infliximab, adalimumab, alefacept, PUVA therapy, UVB therapy, salicylic acid, calcipotriene)
- Systemic corticosteroids or systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs. [REDACTED]

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

- 
- Photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides)
 - More than 10,000 IU/day of Vitamin A supplements
 - Initiation or changes to non-antipsoriatic concomitant medication that could affect psoriasis (e.g., beta blockers, lithium) during the study
 - The use of tanning booths, sun lamps, non-prescription ultraviolet light sources or excessive sun exposure
 - Phototherapy
 - Application of IP to unaffected skin

The treated areas should not be bandaged, covered or wrapped as to be occlusive. The use of hormonal contraceptives should not be initiated, changed or stopped during the study. Subjects should be instructed to minimize exposure to natural sunlight and to use study provided sunscreens of at least SPF 15 and wear protective clothing during the day. Subjects should not allow the IP to come in contact with the eyes, eyelids or mouth, should not use IP on skin that has eczema, and to always wash hands thoroughly after application of IP.

Subjects will be questioned about all prescription and over-the-counter (OTC) concomitant medication use (including vitamins or nutritional supplements) at each study visit. All concomitant medications will be recorded in the subject's source documents. Any subject who has violated any of the listed restrictions may be discontinued from the study. If discontinued, all End of Study/Early Termination procedures (Visit 4 procedures) should be performed.

10.3.4 Withdrawal of Subjects from the Study

Subjects will be advised that they are free to withdraw from the study at any time. Additionally, the sponsor may cease the study at any time. If necessary, the Investigator may withdraw a subject from the study to protect the health of that subject. The clinical study report will include all reasons for early withdrawals.

Reasons for removal may include the following:

- Subject withdraws consent for any reason
- Subject's condition has worsened to the degree that the Investigator feels it is unsafe for the subject to continue in the study
- Lack of treatment effect

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

- Significant adverse event (AE) that could affect the safety of the subject or the validity of evaluation of the subject's clinical state to an extent considered significant by the Investigator
- Subject's IP becomes unblinded
- There is a protocol deviation that, in the Investigator's, Medical Monitor's or Sponsor's opinion, would compromise the safety of the subject or integrity of the data
- The subject is lost to follow-up. The Investigator will document efforts to attempt to reach the subject at least twice by telephone and by a certified follow-up letter before considering that the subject as lost to follow-up
- Pregnancy
- Administrative reasons
- Other (If the reason for withdrawal is not listed, 'Other' will be specified and the reason noted)

Subjects who withdraw or are removed from the study will not be replaced. The Investigator may refer the subject for appropriate care if the subject withdraws due to safety concerns, as applicable. All subjects who are randomized will be included in the safety monitoring tabulating all AEs experienced after dosing until withdrawal from the study.

10.3.5 Early Termination

If a subject terminates from the study early, all efforts will be made to complete Visit 4 study procedures, obtain any outstanding data and collect all IP. For early termination, the Investigator shall fully document the reason for early termination and the date of removal.

In the event that a subject discontinues from the study at any time due to an AE, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a subject, the Investigator should follow the subject until the AE has resolved, has become clinically insignificant, is stabilized, is confirmed to be ongoing at the end of the study, or the subject is lost to follow-up. Should a serious adverse event (SAE) be noted, procedures stated in section 10.7.4 must be followed. Should pregnancy be noted, procedures stated in section 10.7.6 must be followed.

Subjects who discontinue early because of lack of treatment effect after completing four weeks of treatment will be included in the per-protocol (PP) population as treatment failures provided they had no significant protocol deviations (PDs). Any PD that would compromise the integrity of the data will be considered significant.

Subjects who discontinue early due to worsening condition and require alternate or supplemental therapy for the treatment of their plaque psoriasis during the study should be discontinued, included in the PP population analysis as treatment failures (provided they had no significant PDs during their time of study participation), and referred for effective treatment outside of the study.

Subjects who discontinue early for reasons besides lack of treatment effect or worsening of condition should be excluded from the PP population, but included in the modified Intent-to-Treat

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

(mITT) population using the last observation carried forward (LOCF), provided they administered at least one dose of randomized IP and completed at least one post-dose evaluation.

10.4 Treatments

10.4.1 Treatments Administration

At Visit 1, eligible subjects will receive [REDACTED] of randomized IP (Test, Reference or Placebo). [REDACTED] may be dispensed to the subject at the discretion of the Investigator if the subject has a high BSA affected with plaque psoriasis at the time of dispensation that would warrant [REDACTED]. Enough IP should be dispensed to allow the subject to dose daily until the next scheduled visit.

At Visit 2 and Visit 3, subjects who continue to be eligible for continuation in the study can be dispensed [REDACTED], as needed based on the subject's current BSA and the amount of IP remaining from the tube(s) previously dispensed. Further, any empty tubes will be collected at these visits. At Visit 4, all tubes will be collected (used and unused). A subject may return for an Unscheduled Visit at any time, should they require a resupply of IP (i.e., tube lost; all IP used between visits; tube significantly damaged [became punctured]).

The subject will be instructed on when to apply their first dose of IP, which will be considered Day 1. Females of childbearing potential must administer their first dose (Day 1) [REDACTED]

[REDACTED] For all other subjects, the first dose (Day 1) of IP will be applied on the evening of Visit 1.

Subjects will be instructed to apply enough cream (2 mg/cm²) to cover only the lesions with a thin film. If a bath or shower is taken before application, the skin should be dry before applying the cream. Subjects will be instructed to apply the medication once daily, in the evening and to wash hands thoroughly before and after each application. The first dose will be applied on the evening of Day 1. The subject will then continue to apply a thin film (2 mg/cm²) of the product once daily, in the evening, to cover only psoriatic lesions until the evening before Visit 4 (Day 85 ± 4 days).

The amount of IP required for each subject will vary greatly based on the subject's BSA affected with psoriasis at Baseline, as well as their rate of improvement or disease worsening over the course of the study. For subjects with BSA involvement close to 20% at Baseline, it is estimated that up to approximately [REDACTED] may be required for each subject to dose for the full duration of the study (84 days) depending upon their treatment response. Significantly less IP would be required for subjects with BSA involvement close to 2% (approximately [REDACTED]). Therefore, the amount of IP dispensed to each subject will be dependent upon their BSA involvement at Baseline and as the study progresses, at the discretion of the Investigator. Subject kits will each contain [REDACTED] of IP and will be randomized using the [REDACTED] system. After initial assignment of the first kit, additional kits of IP may be assigned to the subject as needed for dosing and/or to replace a missing tube and/or significantly damaged tube (i.e., punctured), also using the [REDACTED] system. [REDACTED]

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

[REDACTED]

At each visit, the subject will be provided with a dosing diary in which they will be required to record the date of Day 1, all dosing dates and times and any missed doses. Each diary should be returned at the following visit so that the study staff may check compliance and file in the subject's source documentation.

10.4.2 Identity of IP

The following products will be used in the study:

- **Test:** Tazarotene Cream 0.05% (Fougera Pharmaceuticals Inc.)
- **Reference:** TAZORAC® (tazarotene) Cream 0.05% (Allergan, Inc.)
- **Placebo:** Placebo (vehicle) Cream (Fougera Pharmaceuticals Inc.)

10.4.3 Study Blind

The sponsor, clinical research organization (CRO), Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the subject's treatment assignment. The subject will be requested not to discuss the appearance of the IP tube with the Investigator or study staff outside of the [REDACTED]. The tubes of Test, Reference and Placebo products will be blinded with identical outer cartons and labels. This will allow the study to be conducted under double-blind conditions (i.e., such that neither the subject nor the Investigator or study staff members will know the identity of the subject's treatment).

Each study site will have an [REDACTED] is blinded to the treatment arm that each subject has been randomized to.

[REDACTED]

To ensure that information that could potentially bias handling of data is not disclosed, access to the master randomization code will be extremely limited. A sponsor representative who is not involved in clinical development or the study conduct will provide initial approval of the final code to [REDACTED] upon code generation. A member of the sponsor Pharmacovigilance department will have access to the code in case of a safety emergency and in order to expedite FDA reporting, if applicable. Otherwise, the packaging company [REDACTED] will hold the master randomization code until after database lock. No parties (CRO, clinical sites or sponsor) involved in the conduct of the study will have access to the master randomization code until after database lock.

Breaking the blind must be considered only when knowledge of the treatment assignment is deemed essential by the Investigator for the subject's care. Whenever possible, if the Investigator feels that

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the subject should be unblinded, the Investigator should contact the [REDACTED] Medical Monitor to discuss the circumstances and come to an agreement before breaking the blind. If the [REDACTED] Medical Monitor cannot be reached, then the [REDACTED] or designee should be contacted before unblinding. [REDACTED] staff will notify the sponsor if they have received any requests to break the blind. This process will be documented, shared with the sponsor and filed.

CRO Contacts

[REDACTED]
[REDACTED]
Cell Phone: [REDACTED]
Phone: [REDACTED]
Fax: [REDACTED]
Email: [REDACTED]

Or:

[REDACTED]
[REDACTED]
Phone: [REDACTED]
Fax: [REDACTED]
Email: [REDACTED]

If a decision is made to unblind the subject, the Investigator will contact the [REDACTED] [REDACTED] telephone number for the subject's treatment assignment information and document the process in the subject's source documentation. The [REDACTED] unblinding telephone number is available 24 hours a day.

[REDACTED]
[REDACTED]

In the event the blind is broken for any reason, the Investigator will notify [REDACTED] as soon as possible, preferably within 24 hours, in writing with the details of the occurrence. [REDACTED] staff will notify the sponsor.

At the conclusion of the study, after the database has been locked, each site will be sent a sealed envelope containing the full study randomization scheme that should be retained with the study documents in the event of an FDA Inspection.

10.4.4 IP Shipment, Retention and Storage

The IP will be shipped to each Investigator's site from [REDACTED], a centralized distribution center. Upon receipt of the IP, the Principal Investigator (or designee), must immediately inventory the material and confirm receipt with the sponsor, per the instructions included in the shipment. [REDACTED]

[REDACTED]
[REDACTED]

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The Principal Investigator at each site will then ensure that all IP is stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). [REDACTED]

[REDACTED] All IP will be stored at 20°C to 25°C (68°F to 77°F), with excursions permitted from -5°C to 30°C (23°F to 86°F). The temperature of the storage location must be monitored on a daily basis and any excursion beyond the required temperature storage range should be reported to the sponsor. An accurate inventory of the IP over the course of the study (i.e., dispensed and returned) will be maintained in accordance with federal regulations.

Initial supply quantities will be based on each site's projected enrollment quantities. Resupply will be conducted as needed based on remaining in-house supply and continued enrollment projections. Multiple full blocks of IP will be included in every shipment to the Investigator. [REDACTED]

[REDACTED]

Once [REDACTED] has notified the site that they may return the IP, all unused tubes/kits and empty or partially used tubes/kits, other than those randomly selected for retention samples, will be returned to the sponsor (or designee). It is important that retention samples not be returned to [REDACTED] the sponsor or the packaging company during or at the end of the study. Sufficient IP must be retained among the sites participating in the study to meet the sample retention requirements as outlined by the FDA.¹⁶

10.4.5 Method of Assigning Subjects to Treatment Groups

The IP will be randomized, packaged and blinded by an [REDACTED]. The randomization code will be generated using a validated computer program. [REDACTED]

[REDACTED] Each site will receive multiple, full blocks of IP in each delivery. The quantity received may vary.

The IP will be [REDACTED]

[REDACTED] Over the course of the study, additional kits may be assigned to the subject using [REDACTED], as needed as determined at the discretion of the Investigator, based on the amount of BSA that remains to be treated. For subjects with BSA involvement close to 20% at Baseline, it is estimated that approximately [REDACTED] tubes, but up to [REDACTED] tubes, may be required for each subject to dose for the full duration of the study (84 ± 4 days) depending

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upon their treatment response. Significantly less IP would be required for subjects with BSA involvement closer to 2% (approximately [REDACTED]). Therefore, the amount of IP dispensed to each subject will be dependent upon their BSA involvement at Baseline and as the study progresses, at the discretion of the Investigator. Each subject will maintain the same treatment assignment throughout the study.

Randomization will be pre-planned according to a computer-generated randomization scheme. The randomization code will be retained within [REDACTED] which is maintained by [REDACTED]. [REDACTED] will also retain the kit boxes numbers supplied to each site and the kit boxes numbers that have been selected for retention and are therefore unavailable for dispensing to subjects.

Each kit and tube will be labeled and contain a unique identifying numbers. [REDACTED]

[REDACTED]

Upon confirmation of subject eligibility, the subject's information (i.e., subject's initials, date of birth, etc.) will be entered into [REDACTED], and the system will assign a [REDACTED] number to the subject based upon a [REDACTED]. [REDACTED] will then assign the subject a [REDACTED] in a blinded fashion at Visit 1. This kit box number will correspond to a specific treatment group within [REDACTED]; however, the treatment group will be unknown to the Investigator, the CRO, the sponsor and the subject. The site will record the randomization number and kit box number in the subject's source documentation and drug dispensing log. The [REDACTED] will then dispense [REDACTED]

[REDACTED]

[REDACTED] At Visit 2 and/or Visit 3 and/or an Unscheduled Visit, additional IP may be dispensed to the subject, as needed. The [REDACTED]

[REDACTED] dispense it to the subject and record the tube number. If an additional kit is required at either of these visits, the subject's information will again be entered into [REDACTED]; however, [REDACTED] will now assign an additional kit containing tubes from the same treatment arm. The same process will be followed for the dispensing and recording of additional kit boxes and tubes. Each subject will maintain the same treatment assignment throughout the study.

10.4.6 Compliance

Subjects will be provided with a diary to record the date of Day 1, the time and date of dosing, any missed doses, other concomitant medications and any AEs. Subjects taking fewer than [REDACTED] or more than [REDACTED] of the required doses over the 84 days \pm 4 days, or who missed scheduled applications for [REDACTED] consecutive days will be considered non-compliant with dosing, and excluded from the PP

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population. Compliance with dosing will be verified by the use of the subject diaries and discussion with the subject. Compliance criteria are as outlined in the table below:

Study Design			Compliance Criteria	
	Treatment Duration	Scheduled Doses		
	84 Days	84		

For subjects who are terminated from the study early, compliance will be determined from their duration in the study, up to the time they are considered early terminated. Subjects taking fewer than [REDACTED] of the required doses will be considered non-compliant with dosing. For example, if a subject is dropped from the study after [REDACTED] days of enrollment and doses [REDACTED] times, then percent compliance is [REDACTED].

10.5 Study Conduct

10.5.1 Visit 1 (Day -14 to Day 1): Screening and Baseline Evaluation

- Informed Consent:** Subjects who are willing to comply with study procedures will read, understand and sign the IRB-approved ICF.
- Medical History, Baseline Demographics and Concomitant Medications:** Review the subject's demographics and medical history including concomitant medication use within the last 6 months.
- Pregnancy Test:** A urine pregnancy test will be required of all female subjects of childbearing potential before randomization.
- Vital Signs:** Blood pressure, pulse, temperature and respiration rate will be recorded for each subject. In addition, height and weight will be measured to calculate total BSA.
- Application Site Reactions:** A Medical Investigator (MD, DO, CRNP or PA) will grade the individual signs and symptoms. This will serve as a baseline for subsequent assessments of application site reactions. See Appendix C.
- Dermatologic Assessment:** A Medical Investigator (MD, DO, CRNP or PA) will identify and measure the target lesion (the most severe lesion at the Baseline visit) and the location of the treatment area. The treatment area will be measured by assessing % BSA affected.
- Investigator's Global Assessment:** A Medical Investigator (MD, DO, CRNP or PA) will confirm the diagnosis of stable plaque psoriasis and perform a severity rating according to the IGA to determine the severity of the plaque psoriasis in the treatment area. See Appendix A.
- PASI Assessment:** A Medical Investigator (MD, DO, CRNP or PA) will perform the PASI Assessment on the target lesion site. See Appendix B.
- Inclusion/Exclusion Criteria Review:** Confirm the subject meets all inclusion criteria and none of the exclusion criteria.

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10. **Randomization:** Eligible subjects selected for enrollment will be assigned a randomization number using [REDACTED].
11. **Dispense IP, Supplies, Subject Instructions and Diary:** Randomized subjects will be allocated a specific kit of IP via [REDACTED]. The site will pull this specific kit for the subject and dispense [REDACTED] tubes, as needed. The site will also dispense study supplies (i.e., sunscreen) and a diary. The site will instruct the subject on the use of the IP, the completion of the diary and review the medications and/or treatments that are prohibited during the study.
12. **First Dose with IP:** The site will instruct the subject on when the first dose of IP will be applied, which will be considered Day 1. The subject will record the date of Day 1 in their diary.

[REDACTED]

For all other subjects, the first dose (Day 1) of IP will be applied on the evening of Visit 1.

10.5.2 Visit 2 (Day 28 ± 4 days): Interim Visit

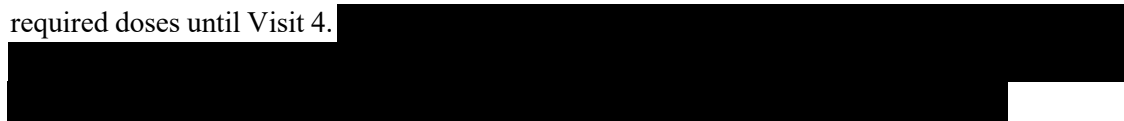
1. **Assess Health Status:** Review the subject's use of any new or ongoing concomitant medications and report any AEs.
2. **Pregnancy Test:** A urine pregnancy test will be required of all female subjects of childbearing potential.
3. **IGA:** A Medical Investigator will perform a severity rating according to the IGA to determine the severity of the plaque psoriasis in the treatment area. See Appendix A.
4. **PASI Assessment:** A Medical Investigator will perform the PASI Assessment on the target lesion site. See Appendix B.
5. **Application Site Reactions:** A Medical Investigator will evaluate any application site reactions since the last visit. See Appendix C.
6. **Collect and Review Subject's Diary:** Collect the diary from the subject and review for compliance with the protocol requirements. If the diary is not returned, the staff will collect available information based on discussion with the subject.
7. **IP Collection, Assessment and Dispensing (as needed):** Review the previously dispensed IP for usage. If a tube is empty, collect it from the subject. If a tube still contains significant product, redispense the tube to the subject. The subject should be dispensed enough IP to complete all required doses until Visit 3. [REDACTED]
8. **Dispense Supplies, Subject Instructions and Diary:** Dispense the study supplies (i.e., sunscreen), as needed and a new diary with Subject Instruction sheet. Re-review proper use of

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the IP, the completion of the diary and the medications and/or treatments that are prohibited during the study.

10.5.3 Visit 3: (Day 56 ± 4 days): Interim Visit

1. **Assess Health Status:** Review the subject's use of any new or ongoing concomitant medications and report any AEs.
2. **Pregnancy Test:** A urine pregnancy test will be required of all female subjects of childbearing potential.
3. **IGA:** A Medical Investigator will perform a severity rating according to the IGA to determine the severity of the plaque psoriasis in the treatment area. See Appendix A.
4. **PASI Assessment:** A Medical Investigator will perform the PASI Assessment of the Target Lesion Site. See Appendix B.
5. **Application Site Reactions:** A Medical Investigator will evaluate any application site reactions since the last visit. See Appendix C.
6. **Collect and Review Subject's Diary:** Collect the diary from the subject and review for compliance with the protocol requirements. If the diary is not returned, the staff will collect available information based on discussion with the subject.
7. **IP Collection, Assessment and Dispensing (as needed):** Review the previously dispensed IP for usage. If a tube is empty, collect it from the subject. If a tube still contains significant product, redispense the tube to the subject. The subject should be dispensed enough IP to complete all required doses until Visit 4. 
8. **Dispense Supplies, Subject Instructions and Diary:** Dispense the study supplies (i.e., sunscreen), as needed, and a new diary with Subject Instruction sheet. Re-review proper use of the IP, the completion of the diary and the medications and/or treatments that are prohibited during the study.

10.5.4 Visit 4: (Day 85 ± 4 days) End of Study Visit or Early Termination

1. **Assess Health Status:** Review the subject's use of any new or ongoing concomitant medications and report any AEs.
2. **Pregnancy Test:** A urine pregnancy test will be required of all female subjects of childbearing potential.
3. **Vital Signs:** Blood pressure, pulse, temperature and respiration rate will be recorded for each subject.
4. **IGA:** A Medical Investigator will perform a severity rating according to the IGA to determine the severity of the plaque psoriasis in the treatment area. See Appendix A.
5. **PASI Assessment:** A Medical Investigator will perform the PASI Assessment of the target lesion site. See Appendix B.

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A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

6. **Application Site Reactions:** A Medical Investigator will evaluate any application site reactions (see Appendix C) since the last visit.
7. **Collect and Review Subject's Diary:** Collect the diary from the subject and review for compliance with the protocol requirements.
8. **IP Collection:** Collect all used and unused tubes and return them to their corresponding kit box(s) for storage. Record any lost or significantly damaged (i.e., punctured) IP.
9. **Discharge from Study:** Discharge the subject from the study.

10.6 Study Procedures

10.6.1 Informed Consent

At Visit 1, before performing any study-related procedures the study subject must sign the IRB-approved ICF. The ICF will be reviewed and approved by an IRB before study commencement. No subject will be entered into the study without reading, understanding and signing an ICF. If the ICF is required in any other language besides English, translation will be performed by a certified translator and then approved by the IRB.

10.6.2 Demographics

At Visit 1, each subject shall be required to provide basic demographic information: date of birth, gender, ethnicity and race.

10.6.3 Medical History

At Visit 1 subjects will be questioned about their personal medical history, including psoriasis history. The medical history will include a complete review of all current diseases and their respective durations and treatments.

10.6.4 Pregnancy Test

All females of childbearing potential will have a urine pregnancy test performed at each visit. The test must be negative at Visit 1 for the subject to be eligible for inclusion in the study. If a subject has to wait for her menstrual period to start before applying the first dose of IP, the first dose of IP must be applied within 14 days of the negative Visit 1 pregnancy test. If the subject is female and not considered of childbearing potential, then the reason must be documented in the subject's source document.

Any subject who becomes pregnant during the study should be discontinued and Early Termination procedures (Visit 4 procedures) completed. Pregnancy reporting procedures should be followed, as outlined in section 10.7.6. The outcome of the pregnancy should be followed by the Investigator to the conclusion of the pregnancy (i.e., birth, termination or miscarriage). The pregnancy will be reported as an AE from the time of first IP dose.

10.6.5 Vital Signs

The subject's vital signs will be recorded (blood pressure, pulse, temperature, and respiration rate) at Visits 1 and 4. At Visit 1, height and weight will also be measured to calculate BSA.

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

10.6.6 Concomitant Medication

At Visit 1, subjects will be questioned about current and prior concomitant medication use over the 6 months before the Baseline visit. Subjects will also be questioned about ongoing or new concomitant medication use during the treatment period at Visits 2, 3 and 4. The medications to be recorded will include prescription and OTC medications and dietary supplements.

At Visits 2 and 3, any subject who has used medications restricted by the protocol may be discontinued from the study. If discontinued, all Early Termination procedures (Visit 4 procedures) should be performed.


10.6.7 Dermatologic Assessment

At Visit 1, the Medical Investigator (MD, DO, CRNP or PA) will assess the subject's plaque psoriasis and calculate the % BSA involvement using the subject's hand (palm plus extended fingers) as an estimate of 1% BSA. For inclusion in the study, % BSA affected must be at least 2% but no more than 20%. The Investigator will then identify and measure the size of the treatment area and identify the most severe psoriasis lesion within the treatment area. This lesion will be designated as the target lesion.

10.6.8 IGA

At Visit 1, a Medical Investigator (MD, DO, CRNP or PA) should document a confirmed diagnosis of stable plaque psoriasis.

At each visit, a Medical Investigator will perform a psoriasis severity rating according to the IGA (see Appendix A). At Visit 1, the IGA must be a score of 3, 4 or 5 for the subject to be eligible for inclusion. At Visit 4 (or Early Termination), the IGA score will be used to determine Treatment Success or Treatment Failure for the primary endpoint, with treatment success defined as none, minimal or mild disease, a score of 0, 1 or 2 within the treatment area. Further, at Visit 4 (or Early Termination), the IGA score will be used to evaluate the secondary endpoint, which is the proportion of subjects with disease severity consistent with none or minimal, a score of 0 or 1, within the treatment area.


The IGA is a static scale and no reference to previous scores for the subject should be made during this assessment.

10.6.9 PASI

At Visit 1, a Medical Investigator (MD, DO, CRNP or PA) will identify the most severe lesion, and this will be designated the target lesion.

At each visit, a Medical Investigator will perform the PASI at the target lesion site according to the PASI scale (see Appendix B). At Visit 1, the PASI score for plaque elevation at the target lesion must be a 3, 4 or 5 for the subject to be eligible for inclusion. At Visit 4 (or Early Termination), the PASI score will be used to evaluate the secondary endpoint, which is the proportion of subjects with target site plaque elevation, scaling and erythema scores of less than or equal to 1.

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

10.6.10 Application Site Reactions

At Visit 1, the Investigator will grade the individual signs and symptoms per Appendix C. This will serve as a baseline for subsequent assessments of application site reactions. At Visits 2, 3 and 4, the Investigator will evaluate the subject for local application site reactions (erythema, dryness, burning/stinging, erosion, edema, pain, and itching) based on the scale provided in Appendix C. Reactions will be documented in source documents for each subject.

10.6.11 Inclusion and Exclusion Criteria Review

At Visit 1, the site will confirm that the subject meets all inclusion criteria and none of the exclusion criteria. If the subject does, they are eligible for enrollment in the study and will be randomized to a treatment group. If the subject does not, their participation will be complete and they will be discontinued as a screen failure.

10.6.12 Randomization

At Visit 1, eligible subjects selected for enrollment will be assigned a randomization number using [REDACTED]. The system will allocate a kit box of IP to the subject in a double-blind fashion. The kit box will contain [REDACTED] of product for a single treatment arm (Test, Reference or Placebo).

10.6.13 Dispensing IP

An [REDACTED] will dispense an initial supply of IP at Visit 1, and will resupply the subject at Visit 2 and/or 3 or an Unscheduled Visit, as needed. The amount of IP dispensed is at the discretion of the Investigator based on the amount of BSA affected with psoriasis. After the initial [REDACTED] of IP have been dispensed and fully used and/or the tube has become lost or significantly damaged (i.e., became punctured), an additional kit box(s) of the same treatment group may be allocated to the subject using [REDACTED].

[REDACTED] will ensure that all Drug Dispensing Logs are completed correctly. Any dispensing task conducted by the [REDACTED], will be verified by a second person using the [REDACTED].

10.6.14 Returning IP

At Visit 2 and/or 3, an [REDACTED] will review the previously dispensed IP. If a tube is empty, it will be collected from the subject. If a tube still contains significant product, the tube will be re-dispensed to the subject. At Visit 4, all used and unused tubes will be collected. The [REDACTED] will ensure that all Drug Dispensing Logs are completed correctly. Any collection task conducted by the [REDACTED], will be verified by a second person using the [REDACTED].

Any lost IP will be recorded in the drug dispensing log and the Comments section of the source document.

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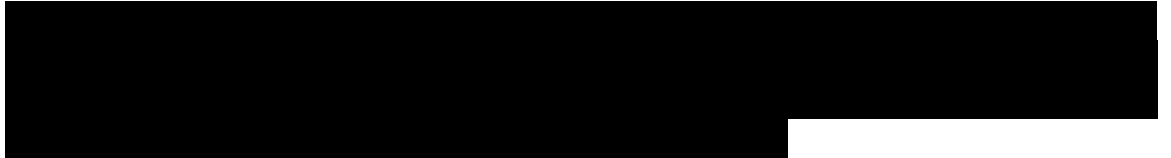
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Any observed tube unblinding will be recorded in the Comments section of the source document and reported to the CRO and sponsor immediately.

10.6.15 Subject Dosing Instructions and Diary

Subjects will be instructed to use the IP as described in section 10.4.1.

The site will instruct the subject on when the first dose of IP will be applied, which will be considered Day 1. The subject will record the date of Day 1 in their diary.



For all other subjects, the first dose (Day 1) of IP will be applied on the evening of Visit 1.

Subjects will be provided with a diary at Visits 1, 2 and 3. Subjects will be asked to record the date of Day 1, the time and date of each dose, any missed doses, any AEs that have occurred and any concomitant medications utilized throughout the study. The site will review the diary and evaluate the subject's compliance with the protocol at Visits 2, 3 and 4, based on any new additions to their medical history, new or changed concomitant medications, AEs and dosing compliance. If the diary is not returned, the staff will collect available information based on discussion with the subject. The subject will also be reminded of the medications and/or treatments that are prohibited during the study.

If the subject is no longer eligible for participation at Visit 2 and/or 3, the site will conduct Early Termination (Visit 4) procedures.

10.6.16 Standardized Sunscreen

Along with the IP at Visit 1, the subject will be provided with standardized sunscreen (Neutrogena Ultra Sheer or similar) for use when needed. The use of the sunscreen should be documented on the concomitant medication page on the source documents and eCRFs. If additional sunscreen is needed during the study, additional sunscreen can be dispensed at Visit 2 and/or Visit 3 or an Unscheduled Visit.

10.6.17 Health Status/AEs

At Visits 2, 3 and 4 subjects will be questioned regarding any changes in their medical status since their previous visit. Any significant health changes observed after signing of the ICF into the study will be reported as AEs, as deemed appropriate by the Investigator.

10.7 AEs/SAEs

The subjects will be monitored throughout the study for any AEs. AEs will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the MedDRA® (Version 18.1 or higher) Adverse Event Dictionary. The subjects will be requested to report signs, symptoms and any changes in health to the clinic staff. Observed changes during the dermatology exam and/or clinical assessment at each visit (i.e., changes in the application site reaction) should be assessed by the Investigator to determine (in their opinion) if the change should be reported as an AE or not. Severity

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of each AE will be determined by the staff based on observation and questioning of the subjects. The Investigator will judge the relationship of the event to the study treatments.

10.7.1 Definitions

An **Adverse Event / Experience** is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An **SAE** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing inpatient hospitalization
- results in persistent or significant disability / incapacity
- is a congenital anomaly / birth defect
- is medically significant: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life- threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

An **Adverse Drug Reaction (ADR)** is any AE for which the Investigator or sponsor assess a reasonable possibility for a causal relationship to a medicinal product, see 10.7.3 below.

An **Unexpected Adverse Reactions** is defined as an ADR, the nature or severity of which is not consistent with the Reference Safety Information (Appendix D). The term ‘severity’ is used here to describe the intensity of a specific event. This has to be distinguished from the term ‘serious’. Reports which add significant information on the specificity, increase of occurrence or severity of a known, already documented serious adverse reaction constitute unexpected events.

Information about common side effects already known about the IP can be found in the Reference Safety Information (Appendix D) or will be communicated in the form of Investigator Notifications. These common side effects are also listed in the informed consent. The common side effects will be discussed with the subject prior to their signing of the informed consent.

For further details, please refer to the “Quick Reference Guide for Completing the SAE Form” for completing the “Serious Adverse Event Report Form” (Novartis form).

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

10.7.2 Severity of AEs

The term ‘severity’ is used here to describe the intensity of a specific event. This has to be distinguished from the term ‘serious’. In the course of the study, the Investigator will determine whether any AE’s have occurred and will grade their severity as follows:

- Mild: Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
- Moderate: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
- Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible

10.7.3 Relationship to the IP

The Investigator should evaluate all AEs considering all accessible data, at any time new information becomes available. The definition of IP includes the Test product under evaluation and the Reference product or Placebo that is given during any phase of the study.

The Investigator should assess whether or not, in his/her expert opinion, the AE is suspected to the drug according to the following considerations:

Suspected:	The temporal relationship of the clinical event to study treatment administration makes a causal relationship possible , and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
Not suspected:	The temporal relationship of the clinical event to study treatment administration makes a causal relationship unlikely , or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Causality assessments are critical and must be provided for each unique AE in relation to each IP. Missing causality assessments will be handled as suspected to IP by the sponsor.

10.7.4 AE Documentation

Any AE (non-serious and serious) occurring after the subject has provided study-specific informed consent, and until the last study visit of the subject, has to be recorded on the AE pages of the eCRF.

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit during the study. AEs also may be identified when they are volunteered by the subject during or between visits or during physical examination, laboratory test or other assessments. All AEs should be given appropriate medical care. Treatment may include one or more of the following: no action taken (i.e., further observation only); IP dosage adjusted/temporarily interrupted; IP permanently discontinued due to this AE; concomitant medication given; non-drug therapy given, subject hospitalized / subject’s hospitalization prolonged. The treatment of the AE should be documented in the eCRF. In addition, the action taken with the IP should be documented, and should be assigned to one of the following categories: not changed, withdrawn, reduced, increased, interrupted,

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

unknown and not applicable. Concomitant medication, other treatments or changes in the administration of the IP should be specified and documented.

Medical conditions/diseases present before starting IP are only considered AEs if they worsen after enrollment. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant or require therapy.

Once an AE is identified, the Investigator should follow-up as specified below. Each time, the outcome should be documented and assigned to one of the following categories: not recovered/unchanged, condition deteriorating, recovered/resolved, improving/recovering, recovered/resolved with sequelae, fatal or unknown. The assessment of an AE should be made at each planned visit (or more frequently, if necessary). The Investigator should document in the eCRF any changes in seriousness, severity, the suspected relationship with the IP, the interventions required to treat it, and the outcome.

AEs occurring between informed consent and first dosing

Any AE occurring between study-specific informed consent and first dosing will be documented as “screening event”, with a IP causality assessment “IP not yet administered”.

AEs occurring after first dosing

The Investigator should follow all AEs which occurred from first dosing and during the course of the study to the last visit of the subject until the AE has resolved or stabilized or the subject has been lost to follow-up.

Ongoing SAEs at the time of last visit

For any SAEs still ongoing at the time of last visit, the Investigator should continue to follow-up until the SAE has resolved or has stabilized / is judged permanent, for SAEs considered to be related to IP (serious adverse drug reaction [SADR]), and for up to 30 days after the last visit of subject for non-related SAEs. The Investigator should send SAE follow-up reports to recipients as per the ‘SAE Reporting’ section 10.7.5 below.

SAEs occurring after the last visit

At the last visit, the Investigator should instruct each subject to report any new SAE (beyond the protocol observation period) that the subject, believes might reasonably be related to study treatment. The Investigator must report the SADR to recipients as per the ‘SAE Reporting’ section 10.7.5 below.

10.7.5 SAE Reporting

It is **vitaly important that the Investigator reports immediately**, (i.e., no later than 24 hours after awareness), any SAEs or updates to previously reported SAEs, even if the Investigator does not consider the AE to be drug-related.

The Investigator should send SAE reports on the “Serious Adverse Event Report Form” (Novartis form), as initial or follow-up reports, via fax or email to the Local Person for Pharmacovigilance (LPPV) (listed below), and in copy to the responsible Medical Monitor/CRO Contact and the sponsor (listed below), to the email addresses provided in the table below.

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

The Investigator should also send all updates / new information on a new SAE Report Form as a follow-up to the previously reported SAE. The follow-up information should describe whether the event has resolved or continues, if a diagnosis is available, if and how it was treated, and whether the subject continued or withdrew from study participation.

Recurrent episodes, complications or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs.

Any new SAE (that is considered completely independent of a previously reported SAE) should be reported as a new and separate initial SAE report.

Any queries from the LPPV, CRO or sponsor regarding SAE reports should be answered by the Investigator within 24 hours.

For more detailed information refer to the “Quick Reference Guide for Completing the SAE Form”.

The Investigator should retain a delivery notification for all recipients in the Investigator study file.

Addresses for SAE and other Safety Reporting	
LPPV, Sandoz (United States)	
Name: [REDACTED]	
Email: [REDACTED]	
Fax: [REDACTED]	
CRO Contacts	
[REDACTED]	[REDACTED]
Cell Phone: [REDACTED]	Phone: [REDACTED]
Phone: [REDACTED]	Fax: [REDACTED]
Fax: [REDACTED]	Email: [REDACTED]
Email: [REDACTED]	
Sponsor Contacts	

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

<p>[Redacted]</p> <p>Phone: [Redacted] Fax: [Redacted] Email: [Redacted]</p>	<p>[Redacted]</p> <p>Phone: [Redacted] Fax: [Redacted] Email: [Redacted]</p>
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The responsible contact persons for questions are:	
<p>[Redacted]</p> <p>Phone: [Redacted] Fax: [Redacted] email: [Redacted]</p>	<p>[Redacted]</p> <p>Phone: [Redacted] eFax: [Redacted] email: [Redacted]</p>

Investigator Notification

If an ADR is not listed in the Reference Safety Information (e.g., Package Insert), the sponsor may urgently require further information from the Investigator for Health Authority reporting.

The sponsor may, if applicable, issue Investigator Notifications of unlisted SADRs (Suspected Unexpected Serious Adverse Reactions [SUSARs]) to all Investigators concerned with any study with the same IP.

The submission of these Investigator Notifications, if applicable, to IRBs is the responsibility of the Investigator or the CRO as stipulated in the study contract.

Health Authority Reporting

The sponsor will submit all reportable cases within the requested timelines to all concerned authorities.

Under 21 CFR 320.31(d)(3), the sponsor or CRO must inform other Investigators involved in the study plus the FDA within 15 days of becoming aware of the occurrence of the SAEs. When a serious AE is death, sponsor or CRO must inform other Investigators involved in the study plus the FDA within 7 days of becoming aware of the event. SAEs that occur with the Test, Reference or Placebo product must be reported.

IRB Reporting

AEs that are evaluated by the Investigator as "Serious" should be reported by the Investigator to the sponsor and CRO within 24 hours, and the IRB as soon as is practically possible, preferably within 24 hours, whether or not they are considered expected or drug-related.

Investigator Safety Reporting Training

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

The Principal Investigator will be trained on the sponsor SAE/AE and pregnancy reporting obligations as defined in the study protocol. Training will be documented.

10.7.6 Pregnancies

Tazarotene may cause fetal harm when administered to a pregnant woman by potentially inducing teratogenic and developmental effect associated with retinoids. Compliance with adequate birth control measures described in this protocol, including a negative pregnancy test before dosing and its commencement during a normal menstrual period, is of paramount importance. The Investigator must report any cases of pregnancy of subjects in the course of a study immediately (within 24 hours) of awareness to the LPPV and with copy to the responsible Medical Monitor/CRO Contact and the sponsor, to the email addresses provided in the table above, as described in section 10.7.5.

[Redacted]

The Investigator should immediately withdraw the subject from the study, and should follow-up each case of pregnancy through the expected delivery date, and report the outcome, including spontaneous or voluntary termination, details of the birth and any birth defects, congenital abnormalities, or maternal and/or newborn complications.

[Redacted]

[Redacted]

[Redacted]

10.7.7 Quality Complaints

In case of quality complaints (technical or transport complaints), the Investigator within 24 hours of learning of its occurrence informs the Medical Monitor/CRO Contact and the sponsor via the email addresses provided in the table above in section 10.7.5. Reporting should include all details relevant to the quality complaint. The monitor/CRO Contact and/or sponsor may reach out to the site for further detail. Any queries from the CRO or sponsor regarding quality complaints should be answered by the Investigator within 24 hours. The Investigator should document the quality complaint in the subject's source document (for subject's specific quality complaints) and/or the Investigator's study file (for site specific quality complaints), as applicable.

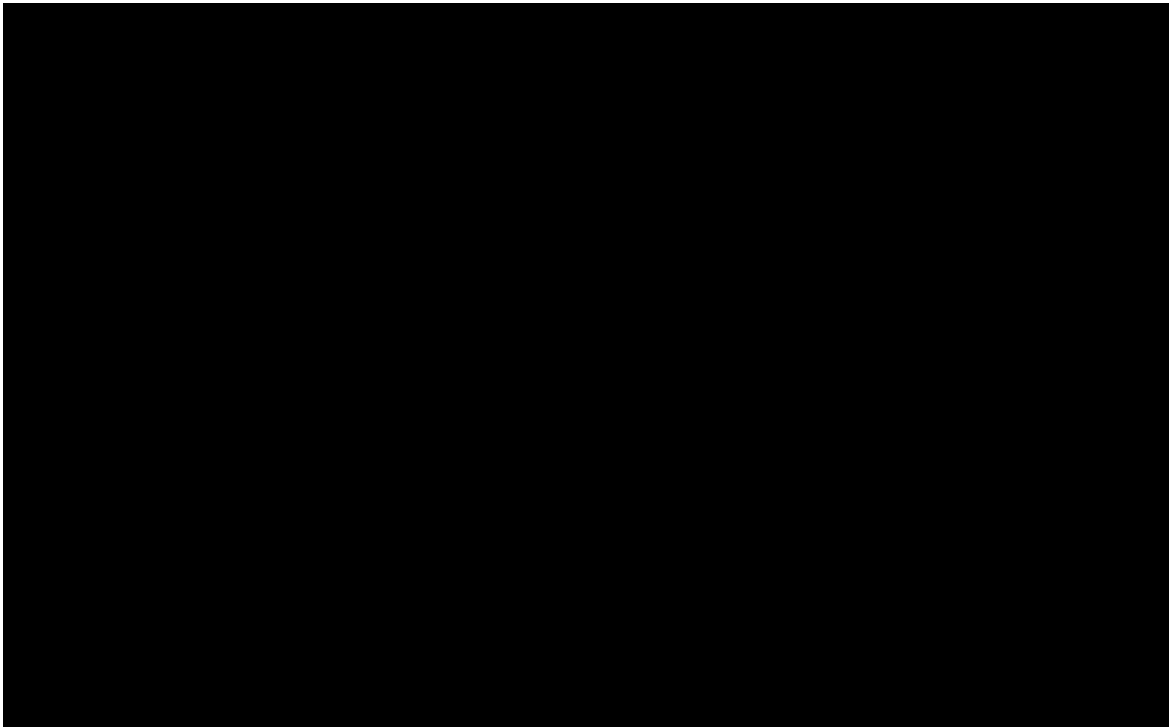
Any AE associated with a quality complaint needs to be documented and reported in addition by the Investigator as described in section 10.7.4 and 10.7.5.

[Redacted]

[Redacted]

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis



10.7.9 Reconciliation

Reconciliation between the safety database of the sponsor and the clinical database at the CRO will be done periodically and at the end of the study by comparing line listings from the safety database with the data in the clinical database.

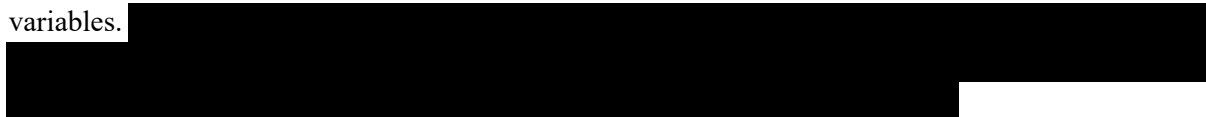
The eCRFs / the clinical database will be reviewed for potentially unreported cases. For any reportable case, the following parameters need to match exactly between the clinical and the safety database: trial number, site number, subject identification number, investigational drug, seriousness, date of death (if applicable) and Investigator causality. All other parameters only need to be plausibly and medically consistent. For any SAE assessed as suspected, a more detailed reconciliation should be conducted, including also treatment dates and medical history.

11.0 STATISTICAL METHODS

11.1 Statistical Plan

A Statistical Analysis Plan (SAP), including study data report format, detailing the intended statistical analysis of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused and spurious data will be included in the SAP.

If not otherwise specified, statistical significance is defined as $p < 0.05$, two-sided. Data will be summarized with respect to demographic and baseline characteristics, efficacy variables and safety variables.



CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

All statistical analysis will be conducted using SAS®, Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC), Study Data Tabulation Model (SDTM) implementation for human clinical trials, and Analysis Dataset Model (ADaM).

11.2 Sample Size Determination

Sample size calculations were performed using [REDACTED]. For the primary endpoint analysis, the rate of treatment success for the Reference treatment after 12 weeks of treatment is expected to be approximately [REDACTED] in the PP population. Assuming that the rates of treatment success for Test and Reference treatments are the same, a sample size of [REDACTED] subjects in each active group in the PP population will provide approximately [REDACTED] power to demonstrate therapeutic equivalence (i.e., the 90% confidence interval (Yates' continuity-corrected) of the absolute difference between the Test and Reference rates of treatment success is within a defined equivalence range [-20% to +20%]).

The rates of treatment success for the Placebo and active treatment groups after 12 weeks of treatment are assumed to be approximately [REDACTED] and at least [REDACTED] respectively, in the mITT population. Using a 1:1 (active: placebo) randomization scheme, and assuming the conversion rate from mITT to PP population will be about [REDACTED] subjects in each treatment group (Test, Reference and Placebo) of the mITT population will provide at least [REDACTED] power to demonstrate superiority of active over Placebo at the 5% significance level ($p < 0.05$, two-sided continuity-corrected Z-Tests and a pooled response rate for the standard error of the difference in proportions).

Under the above assumptions, the overall study power to demonstrate therapeutic equivalence and superiority is estimated to be at least [REDACTED]. To allow for approximately [REDACTED] of subjects who may drop out from the study or are otherwise non-evaluable, up to 855 subjects may be randomized to obtain [REDACTED] subjects in the mITT population (i.e., [REDACTED] per treatment arm).

11.3 Study Populations

11.3.1 PP Population

The PP population will include subjects that comply with the protocol as follows:

- All randomized subjects who meet all inclusion and exclusion criteria.
- Make the final study visit (Visit 4) within the protocol window of Day 85 ± 4 days with no PDs that would affect the integrity of the data.
- Comply with study restrictions including concomitant medications.
- Apply the IP appropriately and are within [REDACTED] compliant with dosing during the 12 weeks (Day 85 ± 4) of treatment.
- Do not miss the scheduled applications for more than [REDACTED]

[REDACTED]

[REDACTED]

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

[REDACTED]

[REDACTED]

11.3.2 Modified Intent-to-Treat (mITT) Population

The mITT population will include all subjects in the PP population plus all randomized subjects who meet all inclusion/exclusion criteria, apply at least one dose of assigned product, and return for at least one post-Baseline evaluation.

[REDACTED]

11.3.3 Safety Populations

All subjects who are randomized and received the IP will be included in the analysis of safety.

11.4 Baseline Comparability

Baseline characteristics will be evaluated separately for the PP, mITT and Safety populations.

The following baseline demographics and parameters (determined from their initial study visit) will be evaluated:

- Age at the time of consent/assent (years)
- Gender (Male/Female)
- Ethnicity (Hispanic/non-Hispanic), Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)
- Baseline total BSA affected with Psoriasis
- Baseline percent BSA affected with Psoriasis
- Baseline PASI Score and Baseline Scores for Individual Components (Erythema, Scaling and Plaque Elevation)
- Baseline IGA Score
- Treatment location
- Treatment area size (area)
- Target lesion size (area)

Summary tables by treatment group will be presented. Continuous variables will be summarized using descriptive statistics (number of observations, median, minimum, maximum, mean and SD). Categorical variables will be summarized using frequencies and percentage. Baseline treatment

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

comparisons will be presented using Chi-Square or Cochran-Mantel-Haenszel tests for the categorical variables, and analysis of variance (ANOVA) for the continuous variables.

All data will be listed by treatment and subject.

11.5 Efficacy Endpoints

Primary Efficacy Endpoint

Proportion of subjects with treatment success (defined as none, minimal or mild disease, a score of 0, 1 or 2 within the treatment area) on the IGA at the Week 12 visit (Day 85 ± 4 days, End of Study).

Secondary Efficacy Endpoints

1. Proportion of subjects with disease severity at the Week 12 visit (Day 85 ± 4 days, End of Study) consistent with none or minimal, a score of 0 or 1, within the treatment area on the IGA, AND
2. Proportion of subjects with target site plaque elevation, scaling and erythema scores of less than or equal to 1 on the PASI at the Week 12 visit (Day 85 ± 4, End of Study).

11.6 Primary and Secondary Endpoint Analyses

Therapeutic Equivalence Analysis

Therapeutic equivalence will be evaluated for both primary and secondary endpoints using the PP population, with results in the mITT population being supportive. For the dichotomized primary endpoint (proportion of treatment success), if the 90% confidence interval (with Yates' Correction Factor) of the difference between the proportion of subjects considered a "treatment success" in the Test and the Reference treatment groups at Week 12 is contained within the pre-defined equivalence limits [-20%, +20%], then therapeutic equivalence will be considered to have been supported for the endpoint. The same statistical approach will be conducted for analysis of the two dichotomized secondary endpoints in the PP and mITT populations.

To declare therapeutic equivalence of the Test product to the Reference product, therapeutic equivalence must be demonstrated for only the primary endpoint in the PP population.

Superiority to Placebo Analysis

The primary measure of superiority will be evaluated using the mITT population and LOCF for missing efficacy values. The results in the PP population will be considered supportive. The superiority of the Test and Reference products over Placebo will be concluded for the primary endpoint if the proportion of treatment success at Week 12 is statistically superior to Placebo ($p < 0.05$, two-sided a Cochran-Mantel-Haenszel exact test stratified by clinical site) using the mITT population and LOCF. The same statistical approach will be conducted for analysis of the two dichotomized secondary endpoints in the mITT and PP populations.

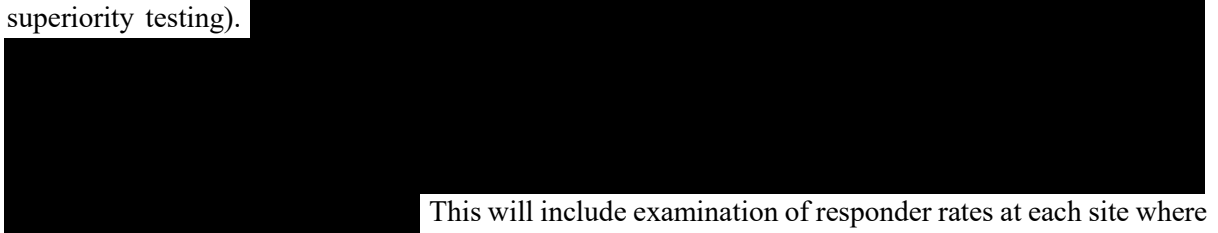
To declare superiority of the Test and Reference products over Placebo, their superiority must be demonstrated for only the primary endpoint in the mITT population.

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

11.7 Treatment-by-Site Interaction and Pooling of Clinical Sites

As this is a multiple-site study, the interaction of treatment-by-site may be evaluated by the Cochran-Mantel-Haenszel test (stratified by site) at the 5% significance level ($p < 0.05$, 2-sided) for the primary efficacy endpoint in both the PP population (for equivalence testing) and mITT population (for superiority testing).

 This will include examination of responder rates at each site where sample sizes per treatment may be influential in the assessment of the interaction.

11.8 Safety Analysis

AEs will be classified using standard MedDRA terminology Version 18.1 or higher and summarized by treatment group. Summary tables comparing the type, date of onset, date of resolution, incidence, severity, relationship to the IP, outcome and action taken will be prepared by treatment group. Should sufficient data exist, AE frequencies will be compared among treatments using Fisher's exact test or a similar test.

Application site reactions (erythema, dryness, burning/stinging, erosion, edema, pain, itching) recorded at each visit will be compared among treatment groups. A descriptive analysis comparing the application site reactions for each treatment group will be created.

Concomitant medication use during the treatment period will be tabulated by subject.

Signs and symptoms of psoriasis will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/subject considers that it is in the subject's best interest to be dropped from continued participation in the study and given alternative therapy for their condition.

All randomized subjects who received IP will be included in the comparative safety analysis.

12.0 REGULATORY OBLIGATIONS

12.1 Institutional Review Board

The study protocol, ICF, subject handouts, if required, and any specific advertising will be submitted to, and approved by, an IRB in writing before the start of the study, as defined by FDA regulations. A form must be issued by the IRB noting the approvals. Based on the IRB's internal policy, the form may be signed by the IRB chairman or designee. The Reference product package insert will also be submitted for the IRB's review. The notification of the board's approval along with a description by profession and gender of the board's composition will be provided to the sponsor.

Any changes to the protocol, as well as a change of Investigator, which is approved by the sponsor/CRO, must also be approved by the IRB(s) and documentation of this approval provided to the sponsor or designee. Records of the IRB review and approval of all documents pertaining to this study must be kept on file by the Investigator and are subject to inspection by regulatory authorities during

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

or after completion of the study. SAEs must also be reported to the IRB per their policy; however, the Investigator/CRO is encouraged to report all SAEs to the IRB as soon as practically possible, preferably within 24 hours, even if the IRB's reporting requirement is longer.

Periodic status reports must be submitted to the IRB per their policy, but at least annually, as well as notification of study completion or termination with a final report within one (1) month after close out. A copy of all reports submitted to the IRB must be sent to the sponsor.

The Investigator will ensure that an IRB that complies with the requirements set forth in Part 56 (Title 21 Code of Federal Regulations) will be responsible for the initial and continuing review and approval of the proposed clinical study.

12.2 Subject Confidentiality

All applicable Investigators and study staff must comply with the federal medical Privacy Rule authorized by the HIPAA), which requires most health care providers to take new measures to protect the privacy of individually identifiable health information. The Privacy Rule's requirements extend to identifiable health information used or disclosed in research. The HIPAA Privacy Rule reinforces clinical Investigators' existing obligations to protect the privacy of identifiable health information under state law, codes of medical ethics and the federal regulations governing research.

Also, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to the sponsor, it is required that the Investigator permit the study monitor, sponsor auditor, and/or FDA representative to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical histories to verify eligibility, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study and autopsy reports for deaths occurring during the study.

As part of the required content of informed consent, the subjects must be informed that his/her medical chart may be reviewed by the sponsor, the sponsor's authorized representatives or FDA. Should access to the medical record require a separate waiver or authorization, it is the Investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

12.3 Study Documentation

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCP) and all applicable regulations, including the Federal Food, Drug and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320, and any IRB requirements relative to clinical studies; and the Declaration of Helsinki, June 1964, as modified by the 64th World Medical Association General Assembly, October 2013.^{8,17-19} The Investigator will permit trial-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data/documents.

12.3.1 Protocol

The Investigator indicated on Form FDA 1572 will act as the Principal Investigator at his/her respective study site. Protocols will be noted as approved by placement of the signatures of the sponsor and [REDACTED] Representatives on the signature page.

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

12.3.2 Informed Consent

An ICF that includes all of the relevant elements currently required by FDA and local state regulations will be provided to each prospective study subject before being screened into the study. The type and method of study, tests to be administered, any potential or possible hazards, and the subject's right to withdraw from the study at any time will be explained to the subjects by the Investigator or designee. Once the Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the subject will be asked to give consent by signing and dating in the appropriate areas of the ICF. The Investigator or designee will also sign and date the form, along with a staff member who will sign the ICF as a witness to verify that the subject has indeed received information. If any other language is required, translation will be performed by a certified translator and will be IRB-approved. A copy of the ICF will be provided to the subject. A notation will be made in the subject's medical record indicating the date informed consent was obtained.

12.3.3 Protocol and Informed Consent Changes

The procedures defined in the protocol will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. Sponsor approved changes to the protocol or the ICF will be implemented as revisions to the original documents and will require additional review and approval by the IRB. Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version. Any revision that substantially alters the study design or increases potential risk to the subject requires the subject's consent to continue in the study. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the sponsor.

The only circumstance in which a protocol amendment may be initiated without prior IRB approval is to eliminate apparent immediate hazards to a subject or subjects. However, the Investigator must notify the IRB immediately, no later than within five (5) working days after implementation.

12.3.4 Source Documents and Case Report Forms

All subjects will be identified by initials and date of birth. Randomized subjects will also have a unique subject randomization number. Source documents will be used to record all study-related data. Source document entries will be used to complete eCRFs which will record all critical study information. A set of eCRFs will be completed for each subject enrolled in the study. All data from eCRFs will be reviewed, evaluated and signed by the Investigator, as required. All eCRFs will be cross referenced to source documentation by the study monitor and/or the sponsor to ensure accurate transcription of the data.

The original source documents and a copy of the corresponding eCRFs (electronic or print out) will be retained by the Investigator. Subjects who terminate early from the study will have the Visit 4 (End of Study/Early Termination) Source/eCRF completed.

Primary Source Documents

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

The Investigator must maintain source documents supporting significant data for each screened subject's medical notes. Standardized source document forms will be utilized for this study and will include original records.

During monitoring visits the monitor will validate data in the eCRFs against the sources of data.

If a subject does not qualify for enrollment, they will be considered a screen failure. The reason for their disqualification will be included in their source document and summarized in the CSR.

Case Report Forms

Source document entries will be used to complete eCRFs for enrolled subjects. All data and eCRFs will be reviewed, evaluated and signed by the Investigator, as required. Further details will be provided in the data management plan.

Supporting Documentation

The Investigator site file will be maintained by the Investigator and study staff and will be available for review during monitoring, auditing and regulatory agency inspections, if applicable.

Details will be provided in the monitoring plan.

12.3.5 Drug Accountability

All IP receipt, inventory, selection of retention, dispensing, dosing and reconciliation records will be maintained in compliance with federal regulations. The IP will be dispensed to qualified study subjects according to established procedures. Drug accountability will be maintained by the site throughout the study, and will be reviewed by the monitor throughout the study. At the end of the study (i.e., at the Site's Close Out visit) all used and unused IP, with the exception of required retention samples, will have a documented inventory conducted and will be returned to sponsor or designee.

12.3.6 Drug Storage

All IP will be stored at 20°C to 25°C (68°F to 77°F), with excursions permitted from -5°C to 30°C (23°F to 86°F). IP should be stored in a secure place with limited access by authorized individuals only. The Investigator will be responsible for maintaining accurate records of IP receipt, retention, dispensing and return.

12.3.7 Retention of Reserve Samples

For every IP shipment received at the Investigator site, the Investigator (or designee) will randomly select one block of IP for retention. As per the Code of Federal Regulations Part 21, Section 320.38(e), "Each reserve sample shall be stored under conditions consistent with the product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used."

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

Instructions on how to select retention samples will be supplied to the Investigator in writing with each shipment, along with a shipment/retention acknowledgment form that must be completed by the study staff and signed by the Investigator. The selection process will ensure a sufficient amount of retention samples are retained as per sponsor requirement. [REDACTED]

[REDACTED] The number of each kit box in the block selected for retention will be noted on the drug accountability form as a retention sample, in addition to the retention sample log and sponsor supplied acknowledgment. These blocks will be affixed with a label provided by [REDACTED] to be clearly marked as retention samples and are not to be used for dispensing to study subjects. Retention samples should not be returned to the sponsor at any time. At the completion of the retention period, the Investigator must contact the sponsor if they wish to destroy the retention samples. If destruction is authorized, the sponsor must supply this directive to the Investigator in writing.

12.3.8 Return of Clinical Supplies

Once authorized by the sponsor, with the exception of the retention samples, all used and unused kits of IP will be inventoried and returned to [REDACTED], who will store the IP until sponsor authorized destruction:

[REDACTED]

12.3.9 Pregnancy and Breastfeeding

Tazarotene cream is designated as Pregnancy Category X; therefore there is a potential risk of teratogenicity. Therefore, all females of childbearing potential should be maintained on an appropriate method of contraception throughout the study to prevent pregnancy. Females that are lactating, breastfeeding or trying to become pregnant should not be enrolled in the study. The ICF will clearly outline the risk and this requirement.

All females of childbearing potential will have a pregnancy test performed at each clinic visit. The pregnancy test will have a minimum sensitivity of at least 50 mIU/ml for hCG. The results of all pregnancy tests (positive or negative) will be documented. A negative urine pregnancy result must be obtained at screening (Visit 1) before study participation. Subjects with a positive pregnancy result during screening will not be enrolled in the study. Before study enrollment, females of childbearing potential must be advised of the importance of avoiding pregnancy during study participation.

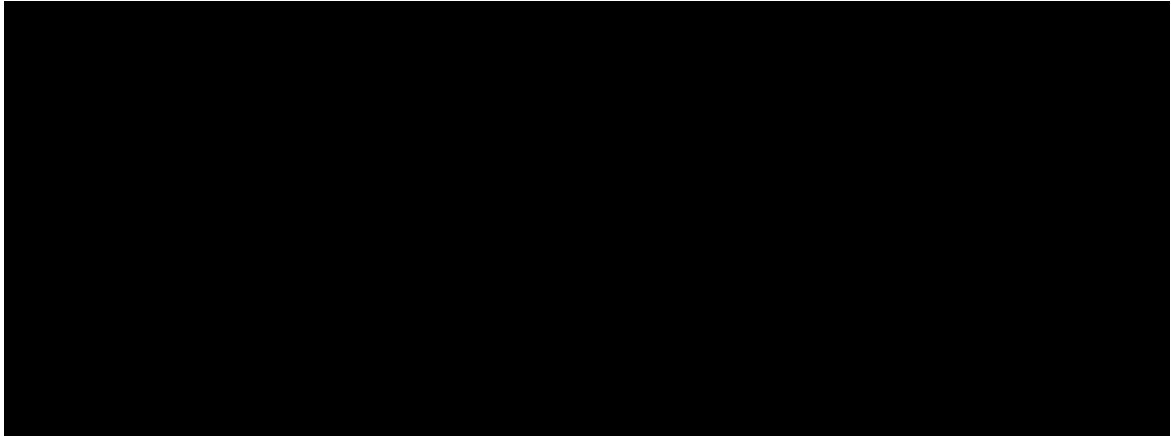
[REDACTED]

Childbearing Potential Defined as:	Non-Childbearing Potential Defined as:
Evidence of menses in the past 12 months	Post-menopausal, defined as women who have been amenorrheic for at least 12

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A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

	consecutive months, without other known or suspected primary cause.
Amenorrhea for \geq 12 months, but the amenorrhea is possibly due to other causes, including prior chemotherapy, anti-estrogens or ovarian suppression	Sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy, or bilateral oophorectomy) with surgery at least 4 weeks before Screening. Tubal ligation will not be considered a surgically sterile method.



Subjects who report that they have become pregnant during the study or have a positive pregnancy test at Visit 2, 3 or 4 will be permanently discontinued from the study utilizing protocol-required procedures for study discontinuation (Visit 4 procedures). The Principal Investigator or designee must immediately notify the Medical Monitor, sponsor LPPV and sponsor representative within 24 hours of learning of the event. The pregnancy will be reported as an AE and all pregnancy reporting criteria will be followed as outlined in section 10.7.6, including the initial use of the [REDACTED] (Novartis form) and all required follow-up for the mother and child as outlined on the form. For more detailed information refer to the [REDACTED]. All follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome will be communicated to the Medical Monitor, sponsor [REDACTED] and sponsor representatives as per the sponsor requirements.

12.3.10 Reporting Safety Information to the IRB

The Investigator must promptly report to the Investigator's IRB all unanticipated problems involving risks to subjects. This includes death from any cause and all SAEs occurring during the study, regardless of the assessed causality.²⁰

12.3.11 Record Retention

The study will be conducted according to GCP as outlined in International Conference on Harmonisation (ICH) step 5 guidelines by the FDA. It is the responsibility of the Investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Investigators will be instructed to retain all study records required by the sponsor, as well as the regulations, in a secure and safe facility, off of the ground, with limited access.

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

All study-related documentation must be retained. This includes, but is not limited to:

- Study Contract
- Study Protocol and all Amendment with Investigator Signature Pages
- Source Data
- eCRFs and Data Queries
- Regulatory Documents
- IRB Documentation (i.e., approvals, correspondence, follow ups, close out)
- IP Receipt and Return Records
- Retention Selection and all IP Accountability Records
- ICFs
- All Logs and Forms
- Monitoring Reports and Letters
- Correspondence

Regulations require the Investigator must retain all records according to 21 CFR 312.62(c) for a period of 2 years following the date the marketing application is approved for the IP for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. However, Fougera requires the Investigator retain all records for a period of [REDACTED] after termination of the study unless CRO or sponsor authorizes, in writing, earlier destruction. No documents shall be transferred from the site (i.e., to an off-site storage facility) without first notifying the sponsor. No documents shall be destroyed without the sponsor's written approval. If the Investigator can no longer support the retention of the records (i.e., due to retirement or death), the documents must be transferred to a new responsible party. The sponsor must be notified of this transfer in writing.

12.3.12 Study Monitoring and Auditing

Monitoring and Auditing by the CRO

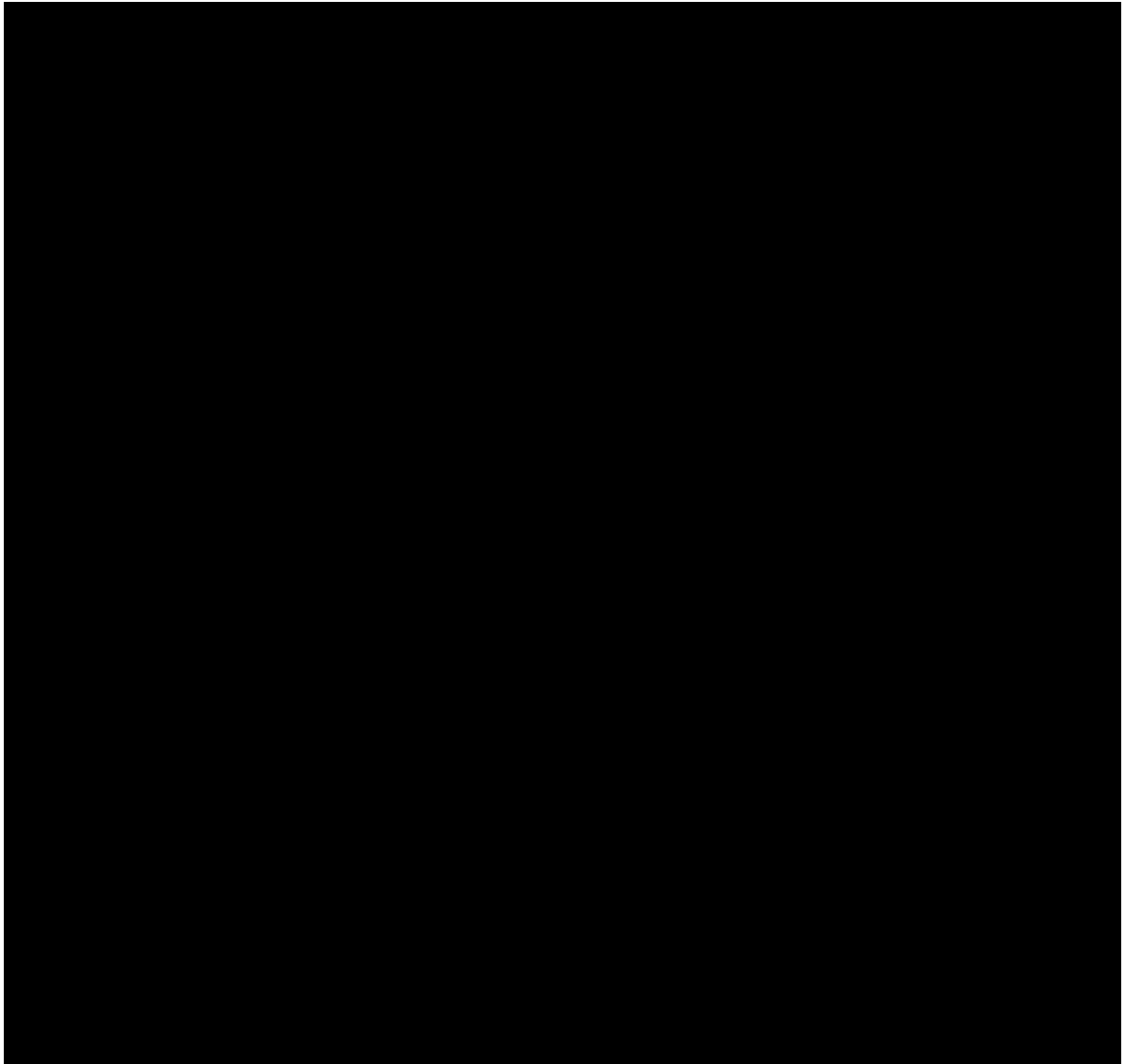
[REDACTED] will be responsible for monitoring the study according to GCP and applicable regulations. Monitoring visits are for the purpose of training, confirming adherence to the protocol and to verify complete and accurate data collection. A monitoring plan will be agreed upon between the sponsor and the CRO. The Investigator will be visited by a monitor before the study, at regular intervals during the course of the study and at the completion of the study. Investigator audits will also be conducted, the details of which would be described in a separate audit plan. Site Monitoring visits and audits (as applicable) will be scheduled with the Investigator in advance of the visit at a mutually agreed time.

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

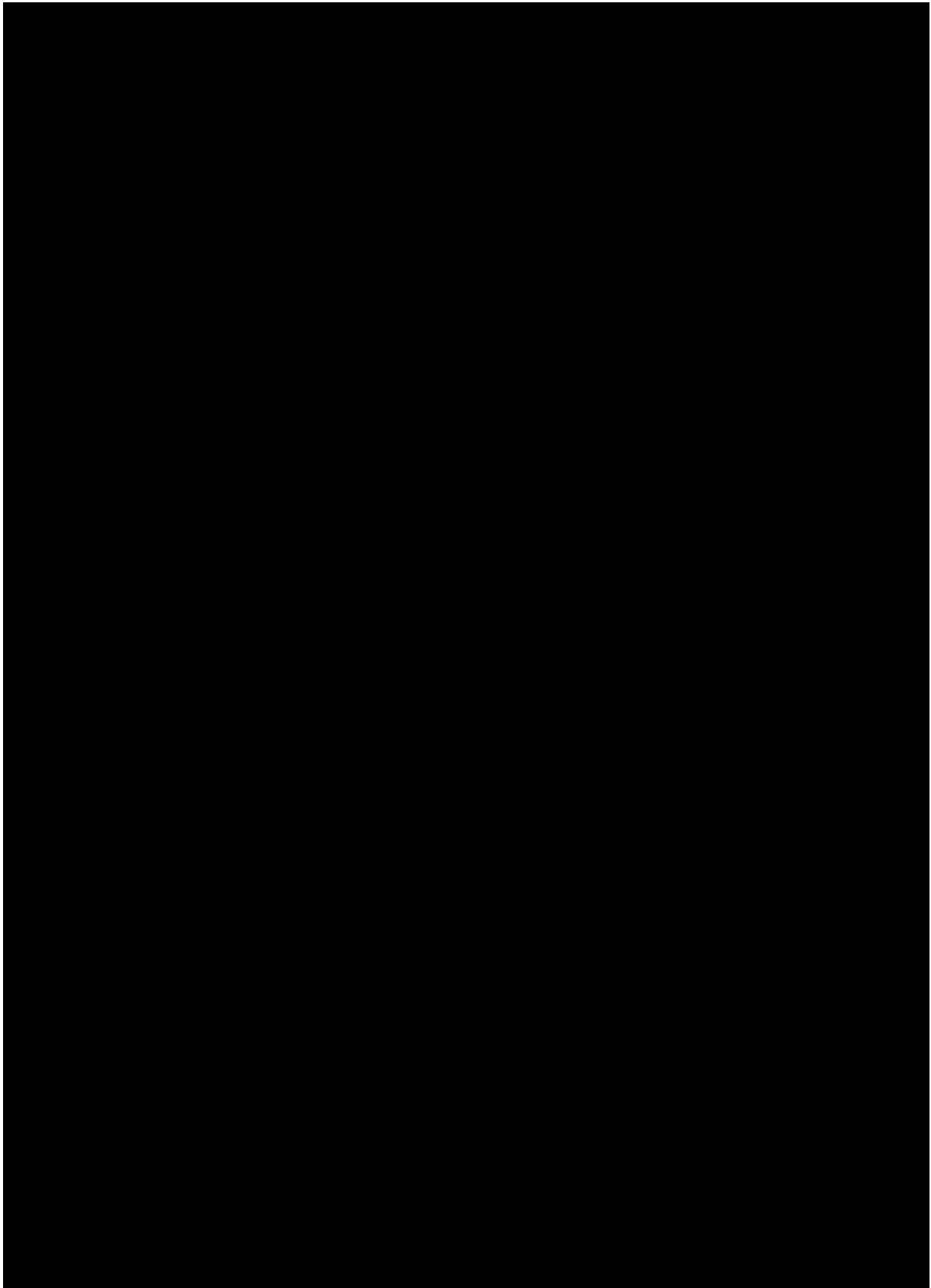
The study monitor will review the ICFs and verify eCRF entries by comparing them with the source documents. The monitor will review the maintenance of regulatory documentation and IP accountability. The monitor will review the progress of the study on a regular basis with the Investigator and other site personnel. The clinical site will make all records associated with the study available to [REDACTED] representative during such monitoring visits and audits. It is the Investigator's responsibility to:

- Provide the monitor with sufficient time to review the eCRFs and relevant source documents
- Be available to answer questions and/or resolve data clarifications and/or implement corrective and preventative actions (as required following a site audit)
- Provide adequate time and space for these visits



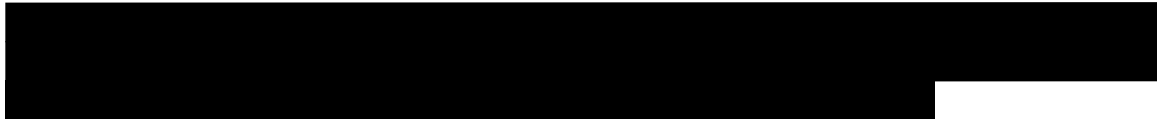
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CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis



Audit by the Sponsor and/or Regulatory Authorities

The study may be subject to audit by the sponsor, sponsor representative, the IRB or by regulatory authorities. The sponsor will schedule any audits in advance of the visit. Regulatory authority audits may take place at any time during or after the study without advance notice. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the sponsor, its representatives and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of study procedures.

12.3.13 Confidentiality, Use of Information and Publication

All information supplied by the sponsor in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, data, materials (i.e., the clinical protocol, eCRFs), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists and technical and commercial information relating to customers or business projections used by the sponsor in its business. Any data, inventions or discoveries collected or developed, as a result of this study is considered confidential. This confidential information shall remain the sole property of the sponsor, shall not be disclosed to any unauthorized person or use in any unauthorized manner without written consent of the sponsor, and shall not be used except in the performance of the study.

The information developed during the course of this clinical study is also considered confidential, and will be used by the sponsor in connection with the development of the drug. The information may be disclosed as deemed necessary by the sponsor. To allow the use of the information derived from this clinical study, the Investigator is obliged to provide the sponsor with complete test results and all data developed in the study. The information obtained during this study may be made available to other Investigators who are conducting similar studies.

The Investigator shall not make any publication related to this study without the express written permission of the sponsor. Should the Investigator wish to publish or present the results of this study, the Investigator agrees to provide the sponsor with an abstract, manuscript, and/or presentation for review ninety (90) days before submission for publication/presentation. The sponsor retains the right to delete from the manuscript confidential information and to object to suggested publication and/or its timing (at the sponsor's sole discretion.)

12.3.14 End of the Trial

Upon a subject's completion in the study, the IP will no longer be available to the subject and all used and unused IP must be collected. The Investigator can, at their discretion, discuss alternative treatments with the subject.

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A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

The end of the trial is defined as the time at which the last subject has completed their last visit in the study. All eCRFs will be completed in compliance with the protocol and all relevant data and/or records will be forwarded to the CRO, as applicable. The Investigator must submit a final report to the IRB. The monitor will conduct a close out visit at the site.

12.3.15 Clinical Study Report

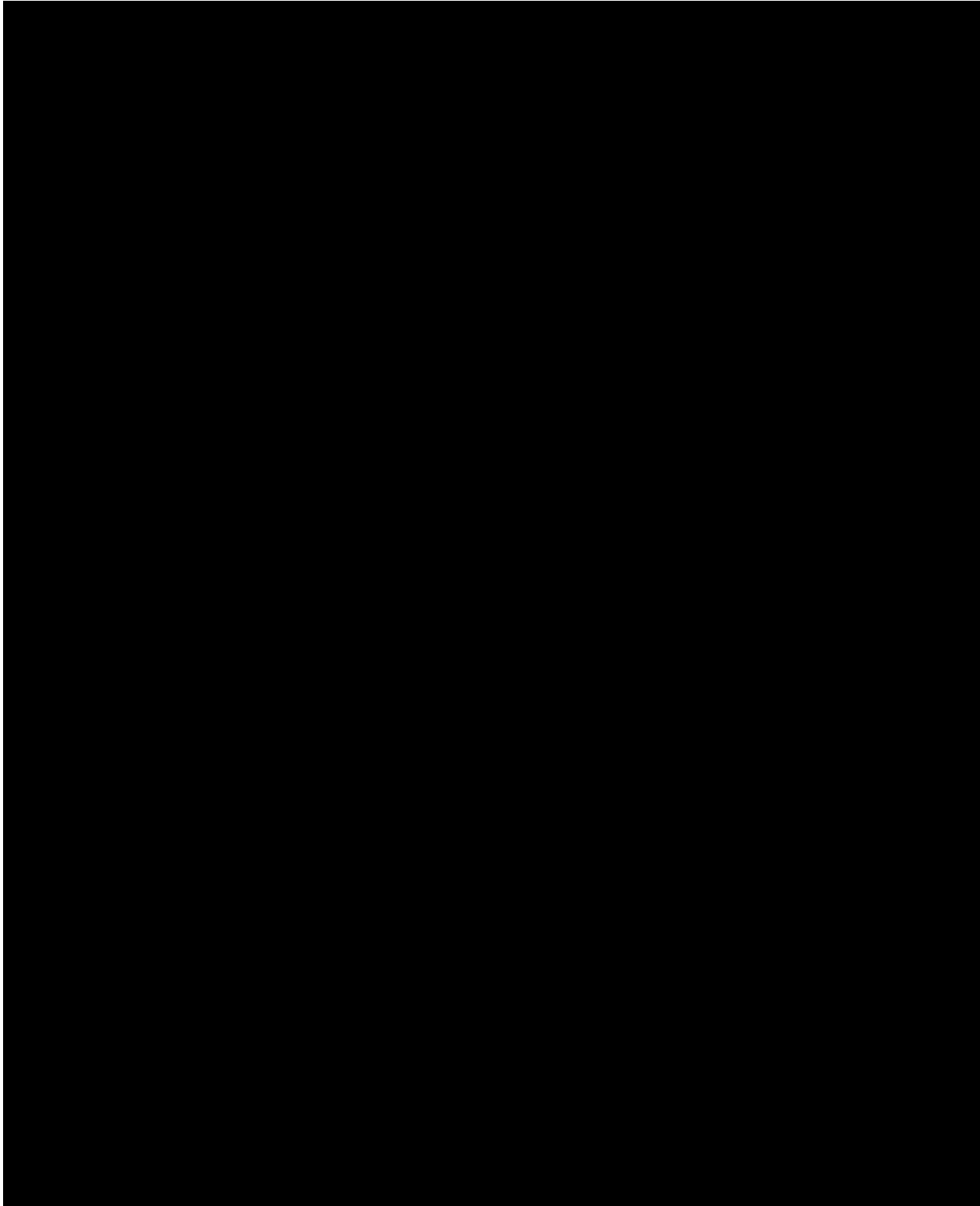
At the end of the study a full report per requirements of sponsor and regulatory authorities will be prepared which will include a narrative of the clinical conduct and results of the study, a statistical report including a description of the analysis performed, and other documentation as may be appropriate. The report will be in electronic format according to eCTD and ICH formatting standards and guidelines.²¹ ANDA summary tables will also be generated. Data sets will be provided in SAS® transport (.xpt) format with appropriate description (Read Me) files as required by FDA.

12.3.16 Termination of the Study

The sponsor reserves the right to terminate the study at any time for administrative or safety reasons. If the sponsor prematurely terminates or suspends the study, or one or more investigative sites participating in the study, the Investigator and/or CRO (as contracted) must promptly inform the IRB. As applicable, the Investigator may be required to follow up on the subject and/or refer them for appropriate care.

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis



CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

14.0 APPENDICES

14.1 APPENDIX A: Investigator's Global Assessment of Disease Severity

Score	Grade	Definition
0	None	No plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale; no erythema
1	Minimal	Essentially flat with possible trace elevation; faint erythema; no psoriatic scale
2	Mild	Slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered
3	Moderate	Moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarse scales with most lesions partially covered
4	Severe	Marked elevation with hard, sharp edges to plaque; severe erythema (very red coloration); coarse, thick scales with virtually all lesions covered and a rough surface
5	Very Severe	Very marked elevation with very hard, sharp edges to plaque; very severe erythema (extreme red coloration); very coarse, thick scales with all lesions covered and a very rough surface

To be eligible for participation in the study a subject must have a Baseline IGA score of 3, 4 or 5.

A subject shall be considered a "treatment success" if he/she has an IGA score of 0, 1 or 2 within the treatment area at the Week 12 visit.

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A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

14.2 APPENDIX B: Psoriasis Area Severity Index at the Target Lesion Site

Score	Grade	Erythema	Scaling	Plaque Elevation
0	Clear	No evidence of erythema	No evidence of scaling	No evidence of plaques above normal skin level
1	Almost Clear	Pink discoloration, minimal erythema	Occasional fine scales hardly noticeable	Slight, just discernible elevation above normal skin level
2	Mild	Light red coloration	Slight but definite roughness, fine scale present, no cracking	Discernible elevation above normal skin level upon examination, but not pronounced
3	Moderate	Moderate redness, but not dark	Moderate roughness, somewhat coarse scaling	Definite plaque formation with rounded/sloped edges to plaque
4	Severe	Dark red coloration	Marked roughness, coarse/thick scaling, cracking may be evident	Marked elevation with hard, distinct edges to plaque
5	Very Severe	Very dark red coloration with induration present	Very thick scales covering extensive area, severe cracking/fissures may be evident	Very marked elevation, very hard and sharp edges to plaque

To be eligible for participation in the study a subject must have a minimum plaque elevation of at least moderate severity (score ≥ 3) at the target lesion site. The most severe lesion at Baseline should be identified as the target lesion.

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14.3 APPENDIX C: Application Site Reactions

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

Signs and Symptoms:

Erythema
Dryness
Burning/Stinging
Erosion
Edema
Pain
Itching

Grading Scale:

<u>Severity</u>	<u>Grade</u>
Absent	0
Mild	1 (slight, barely perceptible)
Moderate	2 (distinct presence)
Severe	3 (marked, intense)

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14.4 APPENDIX D: TAZORAC® (tazarotene) Product Insert

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A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.05% to TAZORAC® (tazarotene) Cream 0.05% and Both Active Treatments to a Vehicle Control in the Treatment of Stable Plaque Psoriasis

14.5 APPENDIX E: Amendments to the Protocol

Amendment	Date
1	12/20/2016

The following revisions were made to the protocol dated 07/26/2016.

- Updated approximate number of sites to be used.
- Section 10.4.5 Black backing on label removed
- Section 10.7.1 Updated reference in Adverse drug reaction section.
- Section 10.7.6 Pregnancy reporting start date clarified; Removed language regarding males impregnating females.

Amendment	Date
2	12/22/2016

- Section 11.6 Updated Cochran-Mantel-Haenszel exact test in Superiority to Placebo Analysis