

CONFIDENTIAL PROTOCOL

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.1% to TAZORAC[®] (tazarotene) Cream 0.1% and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris

1.0 TITLE PAGE

Protocol Title: A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.1% to TAZORAC[®] (Tazarotene) Cream 0.1% and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris

Investigational Product: Tazarotene Cream 0.1%

Population: Approximately 1110 males and non-pregnant females, 12-40 years of age, with acne vulgaris

Study Design: A multi-center, double-blind, randomized, vehicle-controlled, parallel-group bioequivalence study with clinical endpoints comparing Tazarotene Cream 0.1% to TAZORAC[®] (tazarotene) Cream, 0.1% and both active treatments to a vehicle control in the treatment of acne vulgaris

Sponsor: Fougera Pharmaceuticals Inc.

Protocol Number: 0454-01-01 / NCT02886715

██████████ : ██████████

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

Sponsor: Fougera Pharmaceuticals Inc.
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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.

[Redacted Signature]

Date

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PRINCIPAL INVESTIGATOR’S SIGNATURE

I agree to conduct protocol 0454-01-01 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

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5.0 SYNOPSIS

Protocol Number	0454-01-01
Title	A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study Comparing Tazarotene Cream 0.1% to TAZORAC [®] (tazarotene) Cream 0.1% and Both Active Treatments to a Vehicle Control in the Treatment of Acne Vulgaris
Objectives	<ol style="list-style-type: none">1. Evaluate the therapeutic equivalence of the Test product, Tazarotene Cream 0.1% (Fougera Pharmaceuticals Inc.) to the Reference product, TAZORAC[®] (tazarotene) Cream 0.1% (Allergan, Inc.) in the treatment of acne vulgaris.2. Demonstrate the superiority of the efficacy of the Test and Reference (active) products over that of the Placebo in the treatment of acne vulgaris.3. Compare the safety of the Test, Reference and Placebo products in the treatment of acne vulgaris.
Sponsor	Fougera Pharmaceuticals Inc.
Investigational Products	<ul style="list-style-type: none">• Test: Tazarotene Cream 0.1% (Fougera Pharmaceuticals Inc.)• Reference: TAZORAC[®] (tazarotene) Cream, 0.1% (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 \pm 4 days (12 weeks) to the face. Subjects will be instructed to gently clean the face with the provided mild non-medicated cleanser (e.g., Dove [®] Sensitive Skin or similar), pat dry and then apply a thin layer of the product to cover all of the affected skin areas, avoiding contact with the eyes, eyelids and mouth. Hands should be washed before and after each application.
Study Period	84 days (12 weeks) \pm 4 days
Treatment Randomization	2: 2: 1 (Test: Reference: Placebo)
Subject Populations	<p>Approximately 1110 male and non-pregnant female subjects, 12 to 40 years of age inclusive, who meet all of the inclusion criteria and none of the exclusion criteria, will be enrolled in order to obtain ■■■ subjects in the modified Intent-to-Treat (mITT) population and ■■■ subjects in the Per-Protocol (PP) population.</p> <p>The primary inclusion criteria are:</p> <ul style="list-style-type: none">• Clinical diagnosis of acne vulgaris• On the face, \geq 25 non-inflammatory lesions (i.e., open and closed comedones) AND \geq 20 inflammatory lesions (i.e., papules and pustules) AND \leq 2 nodulocystic lesions (i.e., nodules and cysts)

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	<ul style="list-style-type: none">Investigator’s Global Assessment (IGA) of acne severity Grade 2, 3 or 4
Study Design	A multi-center, double-blind, randomized, vehicle-controlled, parallel-group bioequivalence study with clinical endpoints comparing Tazarotene Cream 0.1% to TAZORAC® (tazarotene) Cream, 0.1% and both active treatments to a vehicle control in the treatment of acne vulgaris.
Investigative Sites	Approximately 25 sites in the United States
Study Conduct	<p>Eligible subjects will be randomized in a 2:2:1 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 the first dose on the evening of Day 1 and then continue to apply a thin layer once daily, in the evening, to the affected areas on the face until the evening before End of Study, Visit 4 (Day 85 ± 4 days).</p> <p>Subjects will attend the following scheduled clinic visits:</p> <ul style="list-style-type: none">Visit 1 - Screening/Baseline: Day -14 to 1Visit 2 - Interim Visit: Day 28 ± 4 daysVisit 3 - Interim Visit: Day 56 ± 4 daysVisit 4 - End of Study/Early Termination: Day 85 ± 4 days <p>Efficacy evaluations will be based on dermatological assessments performed in the clinic. The co-primary endpoints, percent change from Baseline in the inflammatory (papules and pustules) and non-inflammatory (open and closed comedones) lesion counts, are to be evaluated at the Week 12 visit (Day 85 ± 4, End of Study).</p>
Inclusion Criteria	<ol style="list-style-type: none">Healthy male or non-pregnant, non-lactating female, ≥ 12 and ≤ 40 years of age with a clinical diagnosis of acne vulgaris.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 

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	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.	[REDACTED]	
	[REDACTED]	
5.	Have facial acne with: ≥ 25 non-inflammatory lesions (i.e., open and closed comedones) AND ≥ 20 inflammatory lesions (i.e., papules and pustules), AND ≤ 2 nodulocystic lesions (i.e., nodules and cysts).	
6.	Have an IGA of acne severity Grade of 2, 3 or 4 (see Appendix A).	
7.	[REDACTED]	
8.	[REDACTED]	

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Exclusion Criteria	<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. Females taking hormonal contraceptives or oral estrogen for less than three months before Visit 1 and those that plan to change the dosage regimen during the course of the study.3. Has more than 2 facial nodulocystic lesions (i.e., nodules or cysts). Any nodules or cysts present will be documented but not included in the inflammatory or non-inflammatory lesion count for analysis.4. [REDACTED]5. Presence of any skin condition that would interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneiform eruptions caused by medications, steroid acne, steroid folliculitis, bacterial folliculitis).6. Has excessive facial hair, such as beards, sideburns, moustaches, etc., that would interfere with the diagnosis or assessment of acne.7. [REDACTED]8. Has active facial sunburn and/or peeling due to sunburn or subjects who will be exposed to excessive sunlight during the study.9. 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 IP.10. [REDACTED]11. History of acne that has been unresponsive to tazarotene and/or other retinoids.12. Use within 6 months before Baseline of oral isotretinoin (Accutane®), oral retinoids (e.g., Soriatane®), or therapeutic vitamin A supplements greater than 10,000 units/day (multivitamins are allowed).13. Use of the following <u>on the face</u> within 1 month before Baseline or during the study:<ul style="list-style-type: none">• Cryodestruction or chemodestruction• Dermabrasion• Photodynamic therapy
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	<ul style="list-style-type: none">• Acne surgery• Intralesional steroids• X-ray therapy <p>14. Use of the following within 1 month before Baseline:</p> <ul style="list-style-type: none">• Spironolactone• Systemic steroids (The occasional use of inhaled, intranasal or ophthalmic corticosteroids for the management of acute and temporary conditions (e.g., allergic rhinitis) and the use of oral acetaminophen for the management of common aches (e.g., headache, menstrual cramps) will be allowed throughout the study to the extent that is acceptable to the Investigator.)• Systemic antibiotics• Systemic anti-inflammatory agents (The use of low dose aspirin for prophylactic use is allowed, provided that the regimen has been stable for at least 3 months before Baseline and will remain constant throughout the study.)• Systemic treatment for acne vulgaris (other than oral retinoids that require a 6 month washout), including anti-androgens <p>15. Use of the following <u>on the face</u> within 2 weeks before Baseline:</p> <ul style="list-style-type: none">• Topical steroids• Topical retinoids• Topical zinc• Topical acne treatments (including over-the-counter (OTC) preparations)• Topical anti-inflammatory agents (including salicylic acid)• Topical antibiotics <p>16. Use of the following <u>on the face</u> within 1 week before Baseline:</p> <ul style="list-style-type: none">• Phototherapy devices for acne [REDACTED]• [REDACTED]• [REDACTED] <p>17. Inability to understand the protocol requirements, instructions and study-related restrictions, the nature, scope and possible consequences of the clinical study.</p> <p>18. Receipt of any drug and/or IP as part of a research study within the 30 days before Baseline.</p>
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	<p>19. 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>20. Previous participation in this study.</p> <p>21. Employees of the Investigator or research center or their immediate family members.</p>										
<p>Efficacy Endpoints</p>	<p><u>Primary Efficacy Endpoints</u></p> <p>The two co-primary efficacy endpoints are (1) the percent change from Baseline to Week 12 in the inflammatory (papules/pustules) lesion counts and (2) the percent change from Baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion counts.</p> <p><u>Secondary Efficacy Endpoint</u></p> <p>The secondary efficacy endpoint is the proportion of subjects who are considered a Clinical Success at Week 12, as defined by an IGA score that is at least 2 grades less than the Baseline assessment. That is, at Week 12, subjects with an IGA score of 4 at Baseline must achieve a score of 0, 1 or 2, subjects with an IGA score of 3 at Baseline must achieve a score of 0 or 1, and subjects with an IGA score of 2 at Baseline must achieve a score of 0 to be considered a Clinical Success.</p> <p>A Clinical Failure is defined as an IGA score at Week 12 that is the same, higher or one grade lower than the Baseline IGA. Subjects who are discontinued due to lack of treatment effect or worsening condition will be considered Clinical Failures.</p>										
<p>Measures</p>	<p>The following scale will be used for evaluation of Baseline disease severity and treatment effect.</p> <p>IGA for Acne Vulgaris</p> <table border="1" data-bbox="500 1318 1401 1812"> <thead> <tr> <th>Grade</th> <th>Description</th> </tr> </thead> <tbody> <tr> <td align="center">0</td> <td>Clear skin with no inflammatory or non-inflammatory lesions</td> </tr> <tr> <td align="center">1</td> <td>Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion</td> </tr> <tr> <td align="center">2</td> <td>Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)</td> </tr> <tr> <td align="center">3</td> <td>Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion</td> </tr> </tbody> </table>	Grade	Description	0	Clear skin with no inflammatory or non-inflammatory lesions	1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion	2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)	3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
Grade	Description										
0	Clear skin with no inflammatory or non-inflammatory lesions										
1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion										
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)										
3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion										

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	<table border="1"><tr><td data-bbox="500 228 678 373">4</td><td data-bbox="678 228 1404 373">Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions</td></tr><tr><td data-bbox="500 373 678 443">5</td><td data-bbox="678 373 1404 443">Greater than Grade 4</td></tr></table> <p>Patients with a Baseline IGA score of 2, 3 or 4 will be enrolled in the study.</p>	4	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions	5	Greater than Grade 4
4	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions				
5	Greater than Grade 4				
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 each treatment’s mean percent change from Baseline to Week 12 in the number of inflamed and non-inflamed lesions.</p> <p>The statistical analyses will involve Analysis of Variance (ANOVA) with terms for treatment and site as fixed effects in the model.</p> <p>Primary Endpoint Analysis</p> <p><u>Therapeutic Equivalence Analysis</u></p> <p>The primary measure of therapeutic equivalence will be evaluated using the PP population, with results in the mITT population being supportive. Under the assumptions of normally distributed data, the adjusted 90% confidence interval will be calculated for the Test/Reference ratio of the mean percent change from Baseline in inflammatory and non-inflammatory lesion counts using an iterative procedure similar to Fieller’s method. ANOVA with treatment and site as fixed effects in the model will be conducted on the mean percent change from Baseline to Week 12 in the inflammatory (papules/pustules) lesion counts and non-inflammatory (open and closed comedones) lesion counts. If the adjusted 90% confidence intervals for the least-squares mean Test/Reference ratios are within 80-125% for both co-primary endpoints, then therapeutic equivalence of the Test to Reference product will be considered to have been demonstrated.</p> <p>To declare therapeutic equivalence of the Test product to the Reference product, therapeutic equivalence must be demonstrated for only the primary endpoints 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, using 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 is concluded if these treatments’ mean percent changes from Baseline in inflamed and non-inflamed lesion counts at Week 12 are statistically superior to that of the Placebo at the 5% significance level ($p < 0.05$, two-sided). The superiority of Test and Reference treatments over</p>				

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	<p>the Placebo will be evaluated in the same ANOVA model for Test vs. Placebo and Reference vs. Placebo.</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> <p>Secondary Endpoint Analysis</p> <p>The PP population will be used for analysis of therapeutic equivalence and the mITT population will be used for analyses of superiority.</p> <p><u>Therapeutic Equivalence Analysis</u></p> <p>For the proportion of Clinical Success, if the 90% confidence interval (with Yates' Correction factor) of the difference between the proportion of subjects considered a Clinical Success in the Test and the Reference product groups at Week 12 is contained within -20% to +20%, then therapeutic equivalence of the Test to Reference product will be considered supported for the secondary endpoint.</p> <p><u>Superiority to Placebo Analysis</u></p> <p>The analyses for superiority will be conducted using the mITT population and LOCF. For the determination of superiority, the proportion of subjects considered a Clinical Success at Week 12 in the Test and Reference product groups will each be compared to the proportion of subjects considered as Clinical Success in the Placebo group.</p> <p>If the proportion of subjects showing Clinical Success in the Test and Reference groups is statistically significantly greater ($p < 0.05$; using Cochran-Mantel-Haenszel exact test stratified by clinical site) than the Clinical Success seen in the Placebo group then superiority will be concluded.</p> <p>A summary table with frequency and percentage of the proportion of Clinical Success by treatment group will be presented.</p>
<p>Safety Analysis</p>	<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>

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	<p>Signs and symptoms of acne vulgaris 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. The electronic case report forms for the study can allow for reporting by Investigators of lesion worsening beyond Grade 4 with treatment. It is recommended that enrollment of acne vulgaris subjects not include subjects with nodulocystic acne. Subjects who worsen beyond Grade 4 will be described in the safety evaluation.</p>
Sample Size Determination	<p>For the primary endpoint analysis (percent change from Baseline at Week 12 (Study Day 85 ± 4 days) in inflammatory and non-inflammatory lesion count), sample size is estimated for therapeutic equivalence of the Test to the Reference product and superiority of each of the active treatments groups over Placebo. As no variability data were available for TAZORAC® cream, 0.1%, the sample size estimations are based on data reported in the [REDACTED]. Sample size calculations were performed using [REDACTED].</p> <p>In the PP population, the mean percent reduction in inflammatory lesion count in the Reference treatment group at Week 12 is expected to be approximately [REDACTED], with a standard deviation (SD) of [REDACTED] (coefficient of variation of [REDACTED]). The mean percent reduction in non-inflammatory lesion count in the Reference treatment group at Week 12 is expected to be approximately [REDACTED] with a SD of [REDACTED] (coefficient of variation of [REDACTED]). Based on these numbers, a sample size of [REDACTED] subjects per active treatment group in the PP population will provide approximately [REDACTED] power to demonstrate that the adjusted 90% confidence interval for the T/R ratio of least-squares treatment means for the primary endpoint is contained within the pre-defined equivalence limits [80%, 125%], if the true ratio is [REDACTED] and assuming [REDACTED] correlation between inflamed and non-inflamed lesion counts.</p> <p>In the mITT population, the mean percent reduction in inflammatory and non-inflammatory lesion counts in the Placebo group is expected to be approximately [REDACTED] ([REDACTED], SD) and [REDACTED] ([REDACTED], SD), respectively. With a conversion rate of [REDACTED] from the mITT to the PP population, [REDACTED] subjects in each active group and [REDACTED] subjects in the Placebo group are required in the mITT population for the superiority analyses. This sample size will ensure sufficient power [REDACTED] to show a difference at $p < 0.05$ (two-sided) between each active treatment group and the Placebo group for each endpoint, assuming [REDACTED] correlation between the inflamed and non-inflamed lesion counts and [REDACTED] correlation between the two superiority tests for each endpoint. Under the above assumptions, the overall study power to demonstrate therapeutic</p>

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	equivalence and superiority for the primary endpoint is estimated to be at least [REDACTED]. To allow for approximately [REDACTED] subjects who may drop out from the study or are otherwise non-evaluable, up to 1110 subjects will be enrolled (444 in each active group and 222 in the Placebo group).
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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/Assent	X [‡]			
Medical History/ Demographics	X [‡]			
Pregnancy Test [†]	X [‡]	X	X	X
Vital Signs	X [‡]			X
Lesion Counts	X [‡]	X	X	X
Investigator's Global 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 through the evening for 84 days (Day 1 to Day 84) 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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7.0 LIST OF ABBREVIATIONS AND TERMS

ADaM	Analysis Dataset Model	OTC	Over-The-Counter
ADR	Adverse Drug Reaction	PD	Protocol Deviation
AE	Adverse Event	PP	Per-Protocol
ANOVA	Analysis of Variance	RLD	Reference Listed Drug
C	Celsius	SADR	Serious Adverse Drug Reaction
CDER	Center for Drug Evaluation and Research	SAE	Serious Adverse Event
CDISC	Clinical Data Interchange Consortium	SAP	Statistical Analysis Plan
CFR	Code of Federal Regulations	SAS	Statistical Analysis Software
CI	Confidence Interval	SD	Standard Deviation
cm	Centimeter	SDTM	Study Data Tabulation Model
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		

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8.0 INTRODUCTION

8.1 Disease Being Treated

Acne vulgaris is a dermatological condition that is characterized by increased sebum production in skin, proliferation of *Propionibacterium acnes* and *epithelial desquamation*. Although most common in teenagers and young adults, it can be a chronic condition that continues throughout adulthood. It is estimated that at least 75% of the adolescent and adult population will show some signs of acne during their lives.²⁻⁵ In the United States, acne is the most common reason for dermatologist consultation. Though signs and symptoms of acne are cosmetically embarrassing and socially stressful, the risk of serious medical complications arising from acne is low.

The clinical appearance of acne can range from very mild (a few comedones on the face) to very severe (large cysts and nodules on the face, chest and back). Subjects selected for this study are considered to have facial acne with ≥ 25 non-inflammatory facial lesions (open and closed comedones), ≥ 20 inflammatory facial lesions (papules and pustules), ≤ 2 facial nodulocystic lesions and an Investigator's Global Assessment (IGA) grade of 2, 3 or 4.

8.2 Availability and Efficacy of Already Approved Therapies

Treatment of acne depends on the severity of the condition, previous treatment regimens and personal preference of the subject. There are a number of different therapies currently available for the treatment of acne. For mild cases, good skin hygiene and over-the-counter (OTC) anti-bacterial washes and scrubs have been shown to control the signs and symptoms. Retinoids, antimicrobials and antibiotics are the mainstay of topical acne therapy. Such treatments are active at application sites, and they can prevent new lesions.⁶ In severe cases, oral antibiotics or retinoids may also be considered if the benefits outweigh the potential risks to the subject.

Tazarotene is one of a class of drugs known as the acetylenic retinoids. Retinoids, such as tazarotene, are the core of topical therapy for acne because they are comedolytic and resolve the precursor microcomedone lesion. The main target of acne treatment is the microcomedone.^{6,7} Tazarotene may also have direct and indirect activity against inflammatory acne. In skin grafts, tazarotene inhibits the expression of a presumed pro-inflammatory marker, migration inhibitory factor related protein type 8 (MRP8), suggesting a direct anti-inflammatory effect. In addition to its effects on the precursor microcomedone lesion, tazarotene allows aeration and release of accumulated sebum by clearing obstructed follicles. This makes the follicles a less hospitable environment for *P. acnes* and indirectly halts the progression to inflammatory acne.⁸

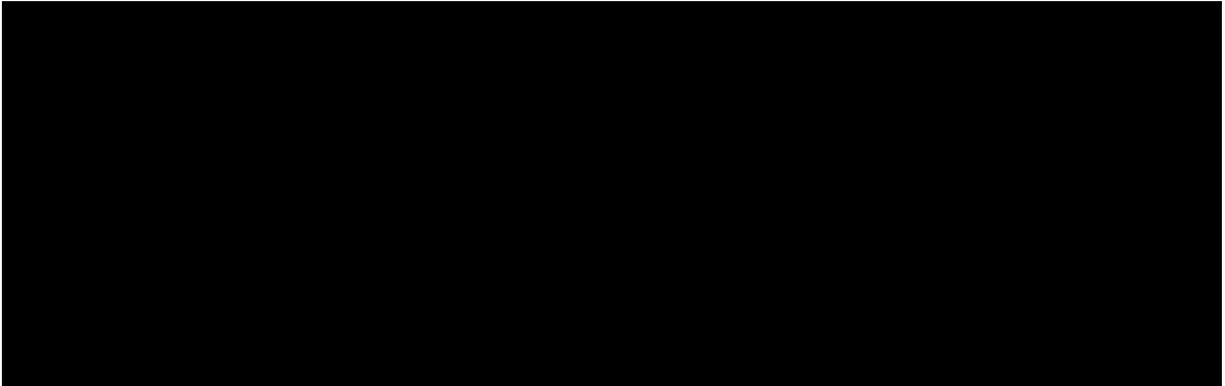
8.3 Scientific and Statistical Considerations

Tazarotene has low systemic absorption and rapid elimination from semi-solid topical formulations of TAZORAC® with mean peak plasma concentrations of tazarotenic acid of 0.10 ng/mL observed on Day 15 following once daily application of tazarotene cream, 0.1% to the face of subjects with facial acne vulgaris.⁹ 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 efficacy can be considered.¹⁰⁻¹² Based on the low systemic bioavailability of tazarotene from the topical

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cream product, a comparative clinical safety and efficacy study is considered the most appropriate method to evaluate the therapeutic equivalence of two tazarotene topical cream, 0.1% 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.^{16,17}

Eligible subjects will have a 20% chance of being randomized to Placebo (2:2:1 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 and Human Services, has issued a detailed guidebook to Institutional Review Boards (IRBs) that includes discussion on the use of placebos in clinical studies.¹⁸

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.

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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 investigational site's 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 0.1% (Fougera Pharmaceuticals Inc.) to the Reference product, TAZORAC[®] (tazarotene) Cream 0.1% (Allergan, Inc.) in the treatment of acne vulgaris.
2. Demonstrate the superiority of the efficacy of the Test and Reference (active) products over that of the Placebo in the treatment of acne vulgaris.
3. Compare the safety of the Test, Reference and Placebo products in the treatment of acne vulgaris.

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 0.1% (Fougera Pharmaceuticals Inc.) compared to the FDA Reference Listed Drug (RLD) TAZORAC[®] (tazarotene) Cream, 0.1% (Allergan) in subjects with a clinical diagnosis of acne vulgaris. Additionally, both the Test product and Reference (i.e., the RLD) product will be tested for superiority to a Placebo. Subjects with confirmed facial acne vulgaris will apply the investigational product (IP) once daily, in the evening, for 84 days \pm 4 days (12 weeks).

Before any study-specific procedures are performed, all subjects will read and sign the IRB-approved ICF. For a subject considered to be a minor in the state he/she is screened, the parent or legal guardian will be required to sign the ICF and the subject will sign an IRB-approved "assent to participate" form, as applicable.

Each site will develop an individualized recruitment plan to collectively enroll approximately 1110 eligible subjects, \geq 12 to \leq 40 years of age, with a clinical diagnosis of acne vulgaris and meeting the inclusion/exclusion criteria. Subjects will be randomized to one of the three IPs as follows:

- **Test:** Tazarotene Cream 0.1% (Fougera Pharmaceuticals Inc.)
- **Reference:** TAZORAC[®] (tazarotene) Cream, 0.1% (Allergan, Inc.)
- **Placebo:** Placebo (vehicle) Cream (Fougera Pharmaceuticals Inc.)

Subjects will attend the following scheduled clinic visits:

- 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

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At Visit 1, eligible subjects will be randomized to the Test, Reference or Placebo product in a 2:2:1 ratio using [REDACTED], which is an interactive response technology (IRT) system provided by the IRT provider. Study subjects will be provided with [REDACTED] of IP. At Visit 2 and/or Visit 3, subjects who continue to be eligible for continuation in the study can be dispensed another [REDACTED] of investigational product, as needed, based on the amount of IP remaining from the tube previously dispensed. Further, any empty tubes will be collect 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 up to [REDACTED] will be needed to dose the subject for the treatment period. Additional tubes beyond the initial [REDACTED] will only be dispensed if the initial supply is lost and/or significantly damaged (i.e., becomes punctured) and warrants replacement.

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 a thin layer (2 mg/cm²) of the product once daily, in the evening, through the evening before Visit 4 (Day 85 ± 4). 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 analyses of interest are (1) the mean percent change from Baseline to Week 12 in the inflammatory (papules/pustules) lesion counts and (2) the mean percent change from Baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion counts. The secondary analysis is the proportion of subjects who are considered a Clinical Success at Week 12, as defined by an IGA score that is at least 2 grades less than the Baseline assessment. A Clinical Failure is defined as an IGA score that is the same, higher or one grade lower than the Baseline IGA at Week 12 (Appendix A).

10.2 Selection of Study Design

This protocol is designed based on studies conducted as a part of the [REDACTED] and the FDA draft guidance for tazarotene cream, 0.1%, released in June, 2011.¹⁹

Statistical analyses of the clinical data will be based on recommendations in the FDA Guidances or communications with the Office of Generic Drugs (OGD)/FDA.^{11,20}

10.3 Selection of Study Population

10.3.1 Inclusion Criteria

1. Healthy male or non-pregnant, non-lactating female, ≥ 12 and ≤ 40 years of age with a clinical diagnosis of acne vulgaris.
2. [REDACTED]

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[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]

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. [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]

- 5. Have facial acne with: ≥ 25 non-inflammatory lesions (i.e., open and closed comedones) AND ≥ 20 inflammatory lesions (i.e., papules and pustules), AND ≤ 2 nodulocystic lesions (i.e., nodules and cysts).

- 6. Have an IGA of acne severity Grade of 2, 3 or 4 (see Appendix A).

- 7. [REDACTED]

- 8. [REDACTED]

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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. Females taking hormonal contraceptives or oral estrogen for less than three months before Visit 1 and those that plan to change the dosage regimen during the course of the study.
3. Has more than 2 facial nodulocystic lesions (i.e., nodules or cysts). Any nodules or cysts present will be documented but not included in the inflammatory or non-inflammatory lesion count for analysis.
4. 
5. Presence of any skin condition that would interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneform eruptions caused by medications, steroid acne, steroid folliculitis, bacterial folliculitis).
6. Has excessive facial hair, such as beards, sideburns, moustaches, etc., that would interfere with the diagnosis or assessment of acne.
7. 
8. Has active facial sunburn and/or peeling due to sunburn or subjects who will be exposed to excessive sunlight during the study.
9. 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.
10. 
11. History of acne that has been unresponsive to tazarotene and/or other retinoids.
12. Use within 6 months before Baseline of oral isotretinoin (Accutane®), oral retinoids (e.g., Soriatane®), or therapeutic vitamin A supplements greater than 10,000 units/day (multivitamins are allowed).
13. Use of the following on the face within 1 month before Baseline:
 - Cryodestruction or chemodestruction
 - Dermabrasion
 - Photodynamic therapy
 - Acne surgery

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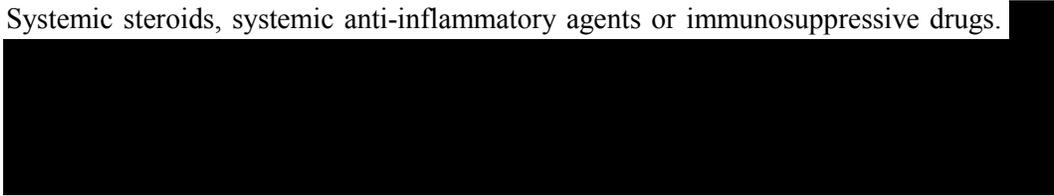
- Intralesional steroids
 - X-ray therapy
14. Use of the following within 1 month before Baseline:
- Spironolactone
 - Systemic steroids [REDACTED]
 - Systemic antibiotics
 - Systemic anti-inflammatory agents [REDACTED]
 - Systemic treatment for acne vulgaris (other than oral retinoids that require a 6 month washout), including anti-androgens
15. Use of the following on the face within 2 weeks before Baseline:
- Topical steroids
 - Topical retinoids
 - Topical zinc
 - Topical acne treatments (including OTC preparations)
 - Topical anti-inflammatory agents [REDACTED]
 - Topical antibiotics
16. Use of the following on the face within 1 week before Baseline:
- Phototherapy devices for acne [REDACTED]
 - [REDACTED]
 - [REDACTED]
17. Inability to understand the protocol requirements, instructions and study-related restrictions, the nature, scope and possible consequences of the clinical study.
18. Receipt of any drug and/or IP as part of a research study within the 30 days before Baseline.
19. Subjects who consume excessive amounts of alcohol, abuse drugs, or have any condition that would, in the Investigator's opinion, compromise compliance with this protocol.
20. Previous participation in this study.
21. Employees of the Investigator or research center or their immediate family members.

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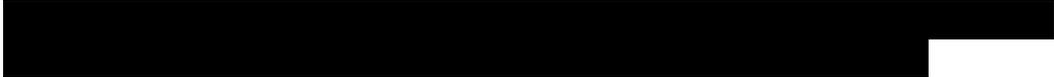
10.3.3 Restrictions During the Study

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

- Use of the following on the face:
 - Cryodestruction or chemodestruction
 - Dermabrasion
 - Photodynamic therapy
 - Acne surgery
 - Intralesional steroids
 - X-ray therapy
 - Topical products applied to the face other than the IP and the study-provided sunscreen and cleanser. Prohibited products include:
 - Moisturizers
 - New brands of make-up
 - Creams, ointments, lotions or powders
 - Medicated cleansers/soaps
 - Medicated shaving products
 - Adhesive strips
 - Any topical product for the treatment of acne applied to the face other than the IP.
 - The use of tanning booths, sun lamps, non-prescription ultraviolet light sources or excessive sun exposure
 - Phototherapy
 - Spironolactone
 - Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed) or other systemic treatment for acne vulgaris
 - Photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides)
 - Systemic (i.e., oral or injectable) antibiotics
 - Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
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- 
- Anti-pruritics including anti-histamines within 24 hours of study visits
 - Any systemic product for the treatment of acne
 - 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 the study-provided sunscreen of at least SPF 15 on the face (as needed). Subjects should not allow the IP to come in contact with the eyes, eyelids or mouth, should not use the IP on skin that has eczema, and to always wash hands thoroughly after application of IP.

Subjects will be questioned about all prescription and 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 and/or assent 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
- Significant adverse event (AE) that could affect the safety of the subject or the validity of the 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

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- 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. In case of 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 a worsening condition and require alternate or supplemental therapy for the treatment of acne 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 (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).

At Visit 2 and/or Visit 3, subjects who continue to be eligible for continuation in the study can be dispensed a [REDACTED] [REDACTED] of IP, as needed, based on the amount of IP remaining from the tube 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]).

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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) during their menstrual period. [REDACTED]

Subjects will be instructed to gently wash the face with the provided mild non-medicated cleanser (e.g., Dove[®] Sensitive Skin or similar), pat dry and then apply a thin layer (2 mg/cm²) of the product to the affected areas of the face, avoiding contact with the eyes, eyelids and mouth.

Subjects will be instructed to apply the IP 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. Subjects will then continue to apply a thin layer (2 mg/cm²) of the IP once daily, in the evening, through the evening before their final visit for a total of 84 days ± 4 days. There will be no application of the product on the day of the End of Study visit.

Subjects will also be instructed not to apply the IP to cuts, abrasions, eczematous skin and sunburned skin and not to use “waxing” as a depilatory method on skin treated with the IP.

Based on an approximate [REDACTED] of cream should be sufficient to last for the full duration of the study (84 days ± 4 days). Subject kits will each contain [REDACTED] of IP and will be randomized using [REDACTED]. If a subject requires additional IP beyond [REDACTED] in order to complete dosing in the study (i.e., tube lost, all IP used between visits or tube significantly damaged [became punctured]), an additional kit of investigational product may be assigned to the subject using [REDACTED].

[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 0.1% (Fougera Pharmaceuticals Inc.)
- **Reference:** TAZORAC[®] (tazarotene) Cream, 0.1% (Allergan, Inc.)
- **Placebo:** Placebo (vehicle) Cream (Fougera Pharmaceuticals Inc.)

10.4.3 Study Blind

The sponsor, contract research organization (CRO), Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the subject’s treatment

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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]. The [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 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]
Cell Phone: [REDACTED]

Phone: [REDACTED]

Fax: [REDACTED]

Email: [REDACTED]

Or:

[REDACTED]
Phone: [REDACTED]

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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 IPs 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]

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] 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]

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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 the kit box number in the subject's source documentation and drug dispensing log. The [REDACTED] will then dispense [REDACTED].

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

[REDACTED] If an additional kit is required at either of these visits, the subject 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 and/or their parent/caregiver 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 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	
[REDACTED]	Treatment Duration	Scheduled Doses	[REDACTED]	[REDACTED]
[REDACTED]	84 Days	84	[REDACTED]	[REDACTED]

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

1. **Informed Consent/Assent:** Subjects who are willing to comply with study procedures will read, understand and sign the IRB-approved informed consent and/or assent, as appropriate. For a subject considered to be a minor in the state he/she is screened, the parent or legal

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- guardian will be required to sign the ICF and the subject will sign an IRB-approved “assent to participate” form, as applicable.
2. **Medical History, Baseline Demographics and Concomitant Medications:** Review the subject’s demographics and medical history including concomitant medication use within the last 6 months.
 3. **Pregnancy Test:** A pregnancy test will be required of all female subjects of childbearing potential before randomization.
 4. **Vital Signs:** Blood pressure, pulse, temperature and respiration rate will be recorded for each subject.
 5. **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 B.
 6. **Investigator’s Global Assessment:** A Medical Investigator (MD, DO, CRNP or PA) will confirm the diagnosis of acne vulgaris and will perform a severity rating according to the IGA to determine the severity of the acne. See Appendix A.
 7. **Lesion Count:** A validated/qualified staff will perform the count of inflammatory lesions (i.e., papules and pustules), non-inflammatory lesions (i.e., open and closed comedones) and nodulocystic lesions (i.e., nodules and cysts).
 8. **Inclusion/Exclusion Criteria Review:** Confirm the subject meets all inclusion criteria and none of the exclusion criteria.
 9. **Randomization:** Eligible subjects selected for enrollment will be assigned a randomization number using [REDACTED].
 10. **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]. The site will also dispense study supplies (i.e., cleanser and 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.
 11. **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.

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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 acne. See Appendix A.
4. **Lesion Count:** A validated/qualified staff will perform count of inflammatory lesions (i.e., papules and pustules), non-inflammatory lesions (i.e., open and closed comedones) and nodulocystic lesions (i.e., nodules and cysts).
5. **Application Site Reactions:** A Medical Investigator will evaluate any Application Site Reactions since the last visit. See Appendix B.
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, re-dispense the tube to the subject. The subject should be dispensed enough IP to complete all required doses until Visit 3. [REDACTED]
[REDACTED] Record any lost or significantly damaged (i.e., punctured) IP.
8. **Dispense Supplies, Subject Instructions and Diary:** Dispense study supplies (i.e., cleanser and/or 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.

10.5.3 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 acne. See Appendix A.
4. **Lesion Count:** A validated/qualified staff will perform count of inflammatory lesions (i.e., papules and pustules), non-inflammatory lesions (i.e., open and closed comedones) and nodulocystic lesions (i.e., nodules and cysts).

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5. **Application Site Reactions:** A Medical Investigator will evaluate any Application Site Reactions since the last visit. See Appendix B.
6. **Collect and Review Subject's Diary:** Collect the diary from the subject and review for compliance with the protocol requirements.
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, re-dispense the tube to the subject. The subject should be dispensed enough IP to complete all required doses until Visit 4. [REDACTED]
[REDACTED] Record any lost IP or significantly damaged (i.e., punctured).
8. **Dispense Supplies, Subject Instructions and Diary:** Dispense study supplies (i.e., cleanser and/or 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 acne. See Appendix A.
5. **Lesion Count:** A validated/qualified staff will perform count of inflammatory lesions (i.e., papules and pustules), non-inflammatory lesions (i.e., open and closed comedones) and nodulocystic lesions (i.e., nodules and cysts).
6. **Application Site Reactions:** A Medical Investigator will evaluate any Application Site Reactions since the last visit. See Appendix B.
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.

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10.6 Study Procedures

10.6.1 Informed Consent and/or Assent

At Visit 1, before performing any study-related procedures the study subject must sign the IRB-approved ICF. For a subject considered to be a minor in the state he/she is screened, the parent or legal guardian will be required to sign the ICF and the subject will sign an IRB-approved “assent to participate” form, as applicable. Both the consent and assent forms 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 informed consent themselves or having their parent/legal guardian conduct on their behalf. If the consent and/or assent are required in any 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 will 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 acne 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 the subject must 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.

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.

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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 IGA

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

At each visit, a Medical Investigator will perform an acne severity rating according to the IGA (see Appendix A). At Visit 1, the IGA must be a score 2, 3 or 4 for the subject to be eligible for inclusion. At Visit 4 (or Early Termination), the IGA score will be used to evaluate the secondary endpoint which is the proportion of subject considered a Clinical Success, with Clinical Success defined as an IGA score that is at least 2 grades less than the Baseline assessment.


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

10.6.8 Lesion Counts

At each visit the number of inflammatory lesions (i.e., papules and pustules), non-inflammatory lesions (i.e., open and closed comedones) and nodulocystic lesions (i.e., nodules and cysts) on the facial area, including the nose, will be counted and recorded. Counts of each lesion type (i.e., inflammatory, non-inflammatory and nodulocystic) should be reported separately in the source and electronic case report form (eCRF). Definitions of these terms are listed in Appendix C.

Lesion counts should only be conducted by those individuals who have successfully completed the lesion count validation. Wherever possible, the same individual should attempt to perform all lesion counts at all visits for an individual subject.

At Visit 4 (or Early Termination), the lesion counts for the inflammatory and the non-inflammatory lesions will be used to evaluate the primary endpoints of percent change in inflammatory lesion counts and percent change in non-inflammatory lesion counts.

10.6.9 Application Site Reactions

At Visit 1, the Investigator will grade the individual signs and symptoms per Appendix B. This will serve as a baseline for subsequent assessments of application site reactions. At Visits 2, 3 and 4, the Medical 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 B. Reactions will be documented in source documents for each subject.

10.6.10 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.

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10.6.11 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).

10.6.12 Dispensing IP

An [REDACTED] will dispense an initial supply of IP at Visit 1, and will resupply the subject at Visit 2, 3 or an Unscheduled Visit, as needed. The subject will initially be dispensed [REDACTED] of IP. When the subject returns for Visits 2 and 3, the amount of IP remaining will be assessed. If a tube still contains significant product, the tube will be re-dispensed to the subject. If an additional tube is required, the tube should be pulled from the allocated kit box. Enough IP should be dispensed so that the subject can complete all required doses until the next scheduled visit.

[REDACTED]

The [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].

10.6.13 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.

Any observed tube unblinding will be reported to the CRO and sponsor immediately.

10.6.14 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.

[REDACTED]

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

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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.

10.6.15 Standardized Cleanser and Sunscreen

Along with the IP at Visit 1, the subject will be provided with standardized mild non-medicated cleanser (Dove Sensitive Skin or similar) and 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 mild non-medicated cleanser and/or sunscreen is needed during the study, additional can be dispensed at Visits 2, 3 or an Unscheduled Visit.

10.6.16 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 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 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

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- 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 on the informed consent. The common side effects will be discussed with the subjects 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).

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 AEs 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.

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The Investigator should assess whether or not, in his/her expert opinion, the AE is suspected to be 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, 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 an IP causality assessment "IP not yet administered".

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Adverse events occurring after first dosing

The Investigator should follow all AEs that occurred from first dosing and during the course of the study to the last visit for the subject, at which point the outcome assessment will be documented in the CRF.

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 [SADRs]), 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.

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

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

The responsible contact persons for questions are:	
[REDACTED]	[REDACTED]
Phone: [REDACTED]	Phone: [REDACTED]
Fax: [REDACTED]	eFax: [REDACTED]
email: [REDACTED]	email: [REDACTED]

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 SADR (Suspected Unexpected Serious Adverse Reaction [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.

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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

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]

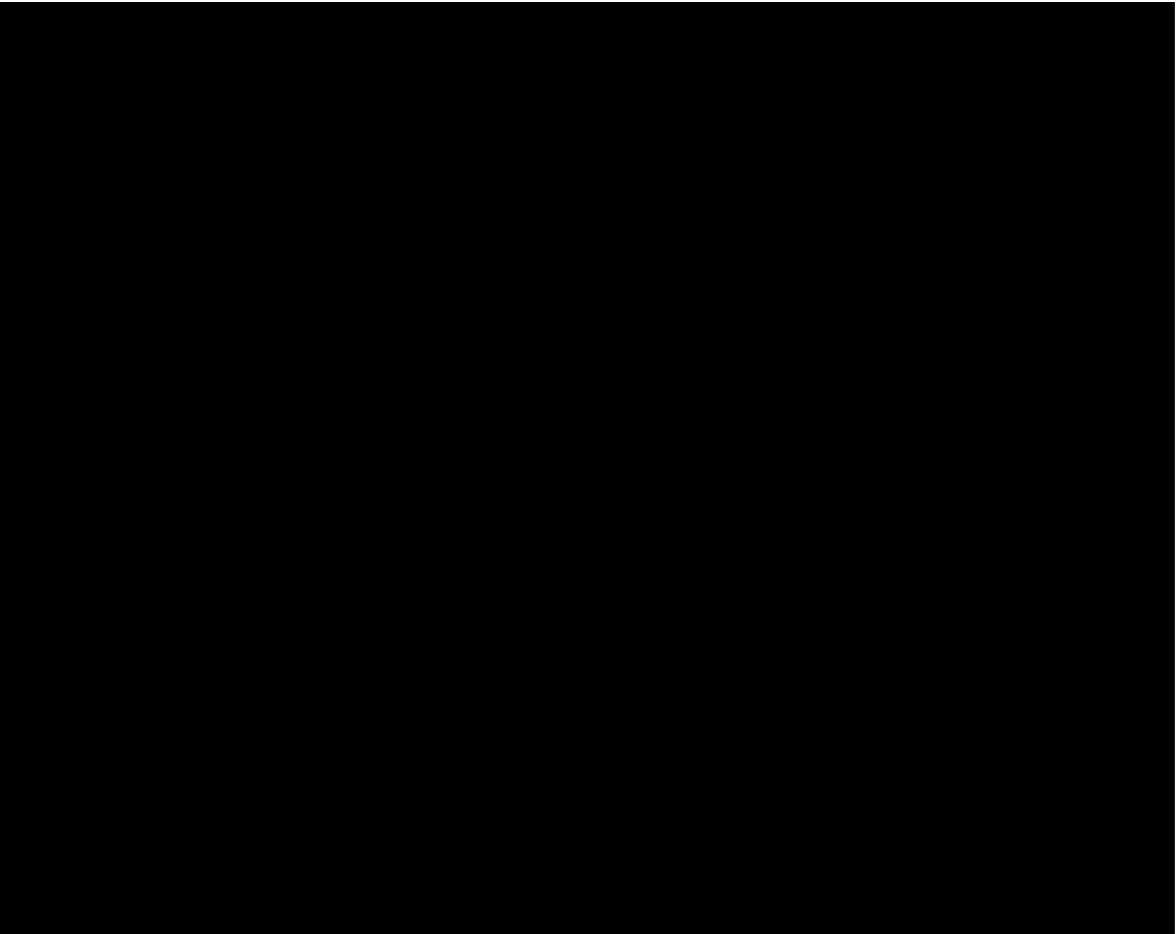
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10.7.7 Quality Complaints

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.



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.

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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.

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

For the primary endpoint analysis (percent change from Baseline at Week 12 (Study Day 85 ± 4 days) in inflammatory and non-inflammatory lesion count), the sample size is estimated for therapeutic equivalence of the Test to the Reference product and superiority of each of the active treatments groups over Placebo. As no variability data were available for TAZORAC[®] Cream, 0.1%, the sample size estimations are based on data reported in the

Sample size calculations were performed using

In the PP population, the mean percent reduction in inflammatory lesion count in the Reference treatment group at Week 12 is expected to be approximately, with a SD of (coefficient of variation of). The mean percent reduction in non-inflammatory lesion count in the Reference treatment group at Week 12 is expected to be approximately, with a SD of (coefficient of variation of). Based on these numbers, a sample size of subjects per active treatment group in the PP population will provide approximately power to demonstrate that the adjusted 90% confidence interval for the T/R ratio of least-squares treatment means for the primary endpoint is contained within the pre-defined equivalence limits [80%, 125%], if the true ratio is and assuming correlation between inflamed and non-inflamed lesion counts.

In the mITT population, the mean percent reduction in inflammatory and non-inflammatory lesion counts in the Placebo group is expected to be approximately (SD) and (SD),

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respectively. With a conversion rate of [REDACTED] from the mITT to the PP population, [REDACTED] subjects in each active group and [REDACTED] subjects in the Placebo group are required in the mITT population for the superiority analyses. This sample size will ensure sufficient power [REDACTED] to show a difference at $p < 0.05$ (two-sided) between each active treatment group and the Placebo group for each endpoint, assuming [REDACTED] correlation between the inflamed and non-inflamed lesion counts and [REDACTED] correlation between the two superiority tests for each endpoint. Under the above assumptions, the overall study power to demonstrate therapeutic equivalence and superiority for the primary endpoint is estimated to be at least [REDACTED]. To allow for approximately [REDACTED] subjects who may drop out from the study or are otherwise non-evaluable, up to 1110 subjects will be enrolled (444 in each active group and 222 in the Placebo group).

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]

[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]

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11.3.3 Safety Populations

All subjects who are randomized and received 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 number of inflammatory lesions (i.e., papules and pustules)
- Baseline number of non-inflammatory lesions (i.e., open and closed comedones)
- Baseline number of nodulocystic lesions (i.e., nodules and cysts)
- Baseline IGA score

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 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 Endpoints

The two co-primary efficacy endpoints are (1) the percent change from Baseline to Week 12 in the inflammatory (papules/pustules) lesion counts and (2) the percent change from Baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion counts.

Secondary Efficacy Endpoint

The secondary efficacy endpoint is the proportion of subjects who are considered a Clinical Success at Week 12, as defined by an IGA score that is at least 2 grades less than the Baseline assessment. That is, at Week 12, subjects with an IGA score of 4 at Baseline must achieve a score of 0, 1 or 2, subjects

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with an IGA score of 3 at Baseline must achieve a score of 0 or 1, and subjects with an IGA score of 2 at Baseline must achieve a score of 0 to be considered a Clinical Success.

A Clinical Failure is defined as an IGA score at Week 12 that is the same, higher or one grade lower than the Baseline IGA. Subjects who are discontinued due to lack of treatment effect or worsening condition will be considered Clinical Failures.

11.6 Primary Endpoint Analysis

Therapeutic Equivalence Analysis

The primary measure of therapeutic equivalence will be evaluated using the PP population, with results in the mITT population being supportive. Under the assumptions of normally distributed data, the adjusted 90% confidence interval will be calculated for the Test/Reference ratio of the mean percent change from Baseline in inflammatory and non-inflammatory lesion counts using an iterative procedure similar to Fieller's method. ANOVA with treatment and site as fixed effects in the model will be conducted on the mean percent change from Baseline to Week 12 in the inflammatory (papules/pustules) lesion counts and non-inflammatory (open and closed comedones) lesion counts. If the adjusted 90% confidence intervals for the least-squares mean Test/Reference ratios are within 80-125% for both co-primary endpoints, then therapeutic equivalence of the Test to Reference product will be considered to have been demonstrated.

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

Superiority to Placebo Analysis

The primary measure of superiority will be evaluated using the mITT population, using 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 is concluded if these treatments' mean percent changes from Baseline in inflamed and non-inflamed lesion counts at Week 12 are statistically superior to that of the Placebo at the 5% significance level ($p < 0.05$, two-sided). The superiority of Test and Reference treatments over the Placebo will be evaluated in the same ANOVA model for Test vs. Placebo and Reference vs. Placebo.

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.

11.7 Secondary Endpoint Analysis

The PP population will be used for analysis of therapeutic equivalence and the mITT population will be used for analyses of superiority.

Therapeutic Equivalence Analysis

For the proportion of Clinical Success, if the 90% confidence interval (with Yates' Correction factor) of the difference between the proportion of subjects considered a Clinical Success in the Test and the Reference product groups at Week 12 is contained within -20% to +20%, then therapeutic equivalence of the Test to Reference product will be considered supported for the secondary endpoint.

Superiority to Placebo Analysis

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The analyses for superiority will be conducted using the mITT population and LOCF. For the determination of superiority, the proportion of subjects considered a Clinical Success at Week 12 in the Test and Reference product groups will each be compared to the proportion of subjects considered as Clinical Success in the Placebo group.

If the proportion of subjects showing Clinical Success in the Test and Reference groups is statistically significantly greater ($p < 0.05$; using Cochran-Mantel-Haenszel exact test stratified by clinical site) than the Clinical Success seen in the Placebo group then superiority will be concluded.

A summary table with frequency and percentage of the proportion of Clinical Success by treatment group will be presented.

11.8 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 in the ANOVA model for evaluations involving the primary efficacy endpoint. [REDACTED]

[REDACTED] If no treatment-by-site interaction is identified with the primary endpoint then no adjustment will be made to any efficacy analysis and treatment-by site interaction will not be included as a term in the statistical models for evaluating therapeutic equivalence and superiority.

11.9 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 acne vulgaris 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 subjects who received randomized IP will be included in the comparative safety analysis. The eCRF for the study can allow for reporting by Investigators of lesion worsening beyond Grade 4 with treatment. It is recommended that enrollment of acne vulgaris subjects not include subjects with nodulocystic acne. Subjects who worsen beyond Grade 4 will be described in the safety evaluation.

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12.0 REGULATORY OBLIGATIONS

12.1 Institutional Review Board

The study protocol, informed consent/assent form, 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 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 visit. 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

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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 (GCPs) and all applicable regulations, including the Federal Food, Drug and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320 and any IRB requirements relative to clinical studies and the Declaration of Helsinki, June 1964, as modified by the 64th World Medical Association General Assembly, October 2013.^{10,22-24} 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 FDA Form 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.

12.3.2 Informed Consent/ Assent

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. Subjects who are considered minors in the state where they are screened will be asked to sign an "assent to participate" form, written in language appropriate for children, as applicable. The minor's parent or legal guardian will sign the ICF. A copy of the ICF and Assent (when applicable) 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 informed consent/assent forms 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 and Assent amendments/revisions, along with letters noting IRB approval, will be submitted to the sponsor.

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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 eCRF, 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

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

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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."

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]

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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.



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 \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.

Female subjects of childbearing potential must have been using and must agree to continue to use accepted methods of birth control, throughout the study. These include:

- Total abstinence with a documented second acceptable method of birth control should the subject become sexually active
- Intrauterine Device
- Double-barrier method (such as condom plus diaphragm with spermicide)
- Oral, transdermal, injected or implanted non-hormonal or hormonal contraceptive, throughout the study (i.e., Norplant®, Depo-Provera®). If the female is using a hormonal contraceptive, the same product must be taken for 3 months before Visit 1.

NOTE: A sterile sexual partner is not considered an adequate form of birth control.

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Subjects who report that they have become pregnant during the study or have a positive pregnancy test at Visits 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 [REDACTED] 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] 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 LPPV 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.²⁵

12.3.11 Record Retention

The study will be conducted according to GCPs 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.

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, Assent Forms
- All Logs and Forms
- Monitoring Reports and Letters
- Correspondence

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Regulations require the Investigator to 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.

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, resolve data clarifications and/or implement corrective and preventative actions (as required following a site audit)
- Provide adequate time and space for these visits

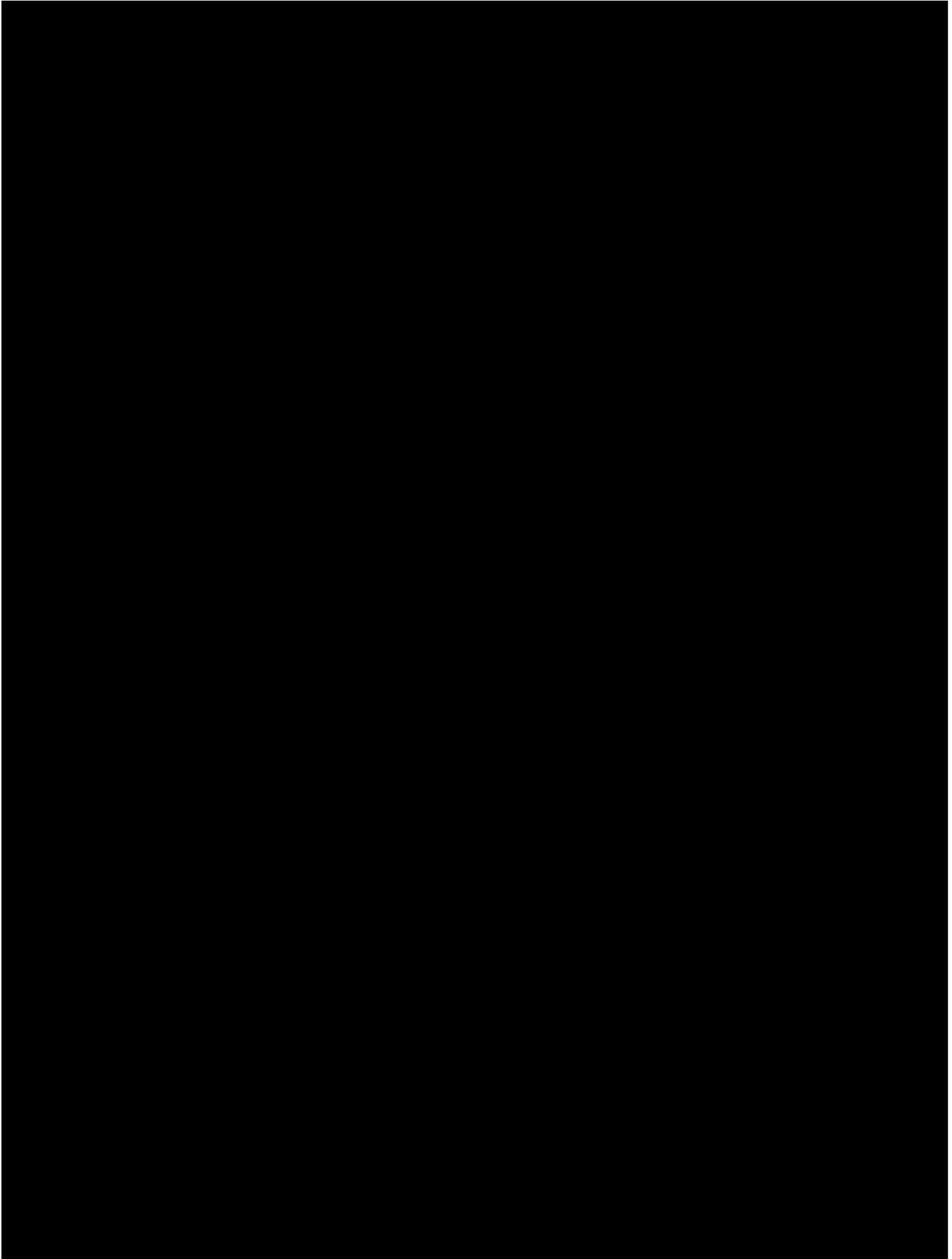
[REDACTED]

[REDACTED]

[REDACTED]

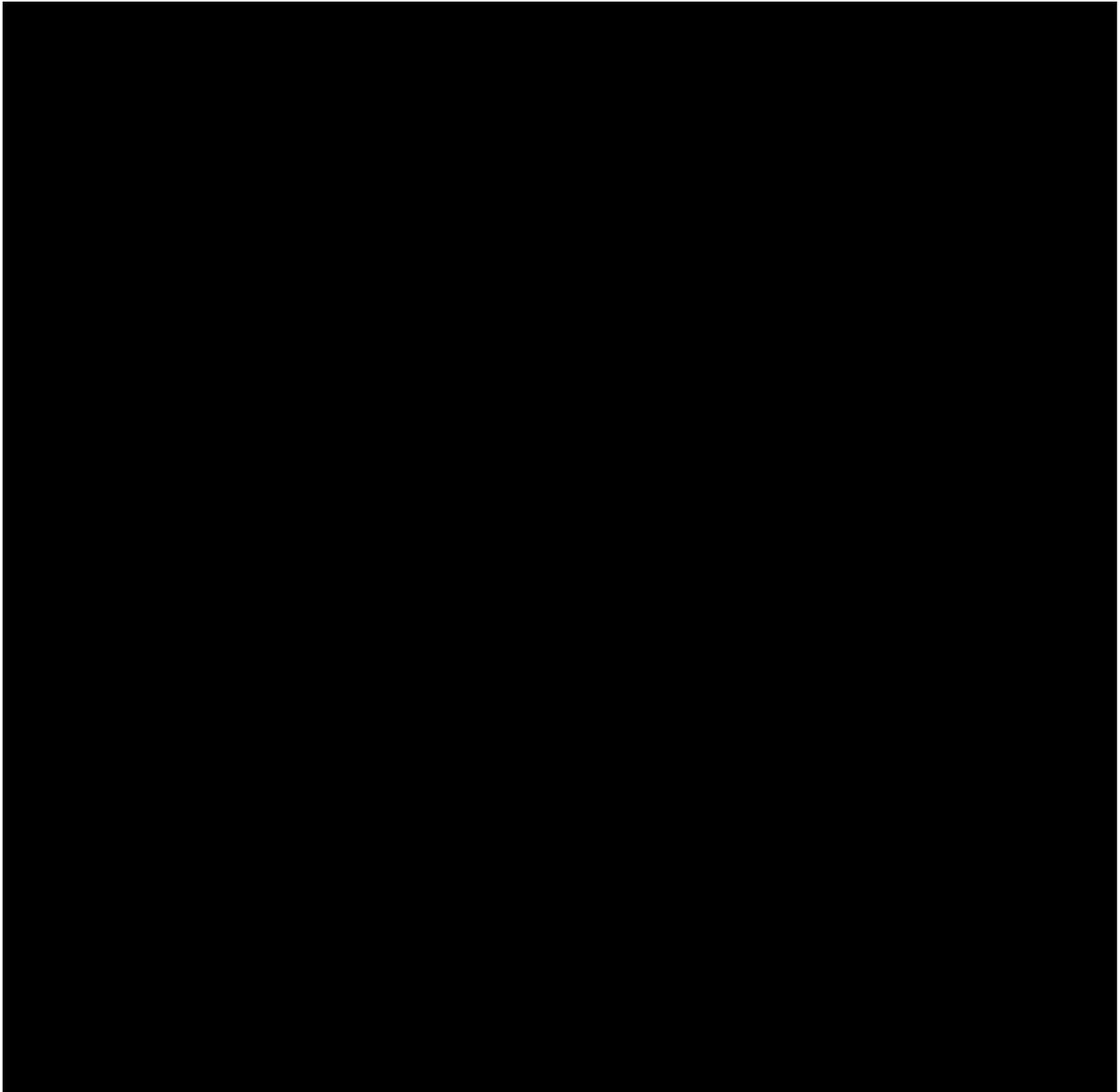
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Audit by the Sponsor and/or Regulatory Authorities

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,

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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.

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 electronic common technical document (eCTD) and ICH formatting standards and guidelines.²⁶ 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.

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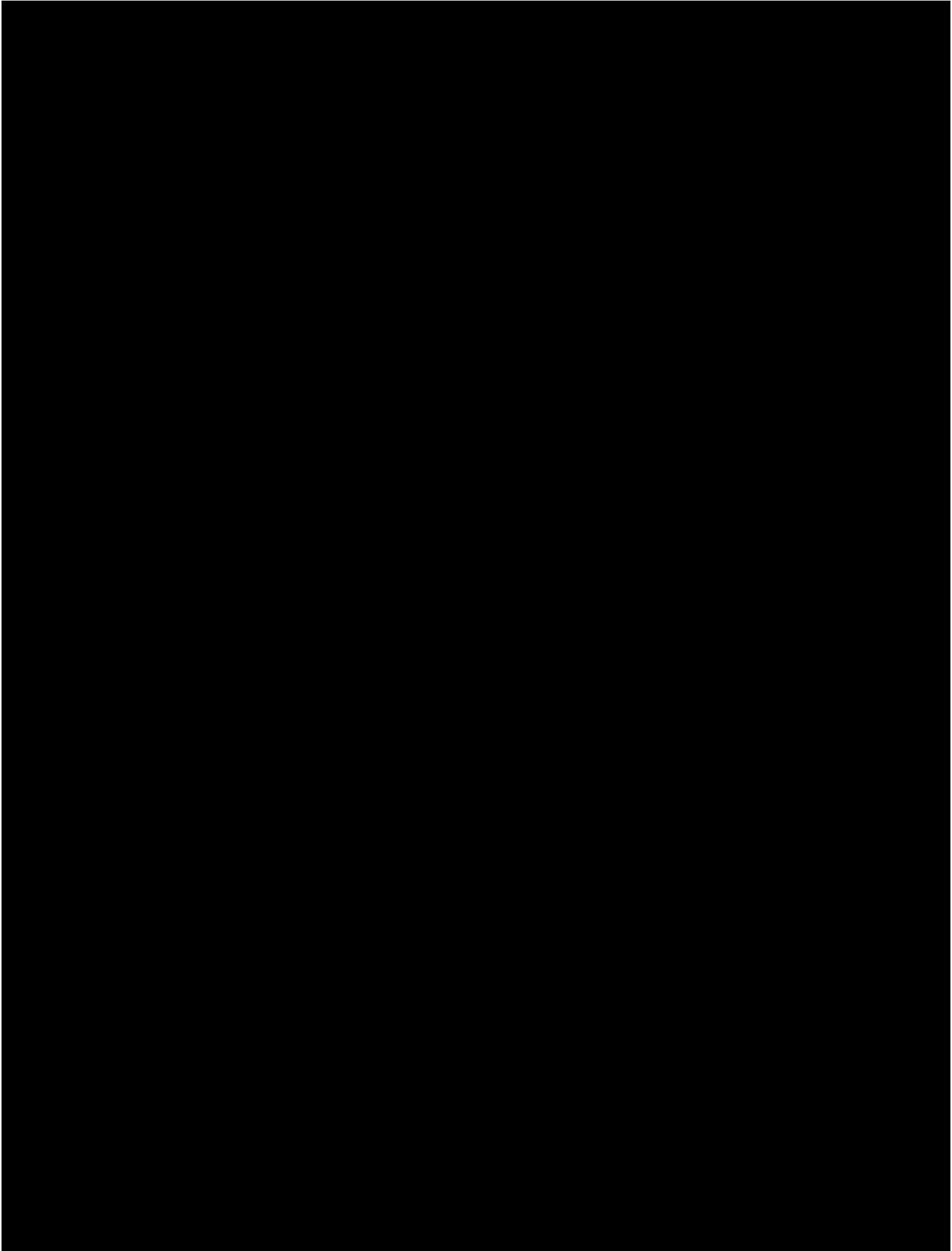
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12.3.16 Termination of the Study

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.

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14.0 APPENDICES

14.1 APPENDIX A: Investigator's Global Assessment for Acne Vulgaris

To be eligible for participation in the study a subject must have a Baseline IGA score of 2, 3 or 4.

Grade	Description
0	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions
5	Greater than Grade 4

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14.2 APPENDIX B: 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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14.3 APPENDIX C: Definition of Terms

Papules: a small circumscribed, superficial, solid, inflamed elevation of the skin that does not contain pus

Pustules: inflamed skin swelling full of pus

Open Comedones: A Widely Dilated Orifice in Which the Pigmented Impaction (Sebum and Keratin) Is Visible at the Skin Surface, Commonly Known As Blackheads

Closed Comedones: Opening Is not Widely Dilated and the Impaction (Containing Sebum and Keratin) Appears As a Small Flesh Colored Papule, Also Known As a Whitehead

Nodules: an inflamed cyst or papule

Cysts: similar to a nodule and often filled with pus

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14.4 APPENDIX D: TAZORAC[®] (tazarotene) Cream, 0.1%[®] Product Insert

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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.		
<ul style="list-style-type: none">• 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	
<ul style="list-style-type: none">• Section 11.7 Updated Cochran-Mantel-Haenszel exact test in Superiority to Placebo Analysis		