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Document: Study Protocol, including Statistical Analysis Plan (SAP)

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Clinical Evaluation of the Sebum Reduction Induced by Clascoterone Cream 1%

STUDY NUMBER	DCS-67-22
INVESTIGATOR	[redacted]
STUDY SITE	Dermatology Consulting Services, PLLC 2444 North Main Street High Point, NC, 27262 [redacted]
INSTITUTIONAL REVIEW BOARD	Allendale Institutional Review Board (AIRB)
SPONSOR	Sun Pharma
STUDY PRODUCT	Winlevi
SPONSOR PRIMARY CONTACT	[redacted]
STUDY DESIGN	Historical control
VERSION NUMBER	2 Amended

PROTOCOL NUMBER: DCS-67-22
PROTOCOL SYNOPSIS AND BUDGET DATE: July 23, 2022
FINAL PROTOCOL DATE: November 20, 2022
AMENDED PROTOCOL DATE: December 15, 2023
STUDY TITLE: Clinical Evaluation of the Sebum Reduction Induced by Clascoterone Cream 1%

The signatures below acknowledge this document represents the final protocol suitable for IRB submission.

[redacted]

1. PROTOCOL SYNOPSIS

Title of Study:	Clinical Evaluation of the Sebum Reduction Induced by Clascoterone Cream 1%
Study Period:	52 weeks (Baseline, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52)
Test Products	Winlevi (Closcoterone Cream 1.0%) Applied to entire face morning and evening.
Objective:	The objectives of this research are as follows: 1. The primary objective is to assess the ability of clascoterone cream 1% to reduce casual facial sebum at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. 2. The secondary objective is to assess the ability of clascoterone cream 1% to reduce casual facial sebum at weeks 2, 6, and 10. 3. The tertiary objective is to demonstrate microbiome changes after 8, 12, and 52 weeks of clascoterone 1.0% facial application.
Design:	Female and male subjects will be enrolled in this single site study to evaluate the effect of closcoterone cream 1.0% on facial sebum production and acne. Subjects who sign consent and meet all inclusion criteria and none of the exclusion criteria will be enrolled at the baseline visit. Subjects will use their own approved skin care products unchanged for the duration of the study. At baseline visit, subjects will receive the study product. The dermatologist investigator will assess facial appearance in terms of oily appearance, pore size, and facial shine. In addition, she will perform a global acne assessment (IGA), inflammatory lesion counts (papules, pustules) and non-inflammatory lesion counts (open comedones, closed comedones). The dermatologist investigator will assess the tolerability criteria of peeling, dryness, redness, and swelling on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe). Three casual sebumeter measurements will be taken from the central forehead 2-4 hours after the subjects washed prior to presenting to the research center. Subjects will assess the performance of their acne treatment regimen by completing a consumer self-assessment/treatment perception questionnaire provided by the sponsor and a tolerability assessment in terms of stinging, itching, and burning. All tolerability assessments will be made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at each visit. Subjects will be given their diaries and study products and asked to return to the research center in 2 weeks. A reminder text will be sent to

	encourage compliance prior to the week 2 visit. Subjects will return to the research center at Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52 for the same assessments. Old study product and diaries will be collected and new diaires and study product dispensed as needed. All the same assessments will be performed as at baseline for all visits. Subjects will continue participation for 52 weeks, at which time their study participation will be completed. Microbiome swabbing for analysis by [redacted] will be obtained from all 40 subjects at baseline, week 8, week 12, and week 52. *(There is an allowance for an unscheduled visit at any time, if necessary.)*
Study Population:	Healthy female and male subjects 12+ years of age Fitzpatrick skin types I-VI with mild to moderate acne (10-100 total non-inflammatory lesions (open comedones and closed comedones), 10-50 total inflammatory lesions, no cysts, and up to 2 nodules (if deemed appropriate by the PI) on the face.
Number of Subjects:	40 subjects
Inclusion Criteria:	1. Males and females 12+ years of age. 2. Subjects with mild to moderate acne. 3. Subjects must possess 10-100 total non-inflammatory lesions (open comedones and closed comedones), 10-50 total inflammatory lesions, no cysts, and up to 2 nodules (if deemed appropriate by the PI) on the face. 4. Subjects with all Fitzpatrick skin types I-VI. 5. Subjects who agree to use only the study products for acne treatment. No other medicated cleansers or moisturizers or acne treatments of any kind are allowed. 6. Subjects agree not to introduce any new colored cosmetics or skin care products while participating in the study (lipsticks, eye shadows, facial foundations, blush, powder, cleansers, moisturizers). 7. Subjects agree to arrive at all visits with a clean face, having washed his/her face and removed all facial and eye makeup products within 2 hours to 4 hours prior to the visit and is not to use/apply any topical facial product(s) until the visit is completed. 8. No known medical conditions that, in the investigator's opinion, may interfere with study participation. 9. Women of childbearing potential must be willing to use a form of birth control during the study. For the purpose of this study, the following are considered acceptable methods of birth control: oral contraceptives, Norplant®, Depo-Provera®, double barrier methods (e.g., condom and spermicide) and abstinence. 10. Subjects are dependable and able to follow directions and willing to comply with the schedule of visits.

	11. Subjects in generally good physical and mental health. 12. Able to read, write, speak, and understand English 13. Individual (and/or his/her legally acceptable representative, as applicable) has signed the Consent for Photograph Release and ICD (and/or Assent Document, as applicable) including Health Insurance Portability and Accountability Act (HIPAA) disclosure. 14. Subject must avoid sun exposure, or use sunscreen if sun exposure is unavoidable. 15. Subject must avoid professional or facial spa procedures during the study.
Exclusion Criteria:	1. Any dermatological disorder, which in the investigator's opinion, may interfere with the accurate evaluation of the subject's skin characteristics, except for the study condition of acne. 2. Subjects who are not willing to use the assigned study product to their face as instructed. 3. Subjects who have acne nodules/cysts representative of severe acne. 4. Subjects who are currently using, planning to use during the study or has used any of the following in the specified time range (based on subject report): - **1 month prior to Visit 1**: Prescription (oral or topically applied on the face) antibiotics, inhaled steroids (except those prescribed for allergies), or hormones (pre- or post-menopausal hormone-replacement therapy; insulin, etc.), or other medications that could make skin more sensitive or have an effect on the skin, as determined by the PI or designee. Oral contraceptives are acceptable. - **1 month prior to Visit 1:** Prescription medication for acne (e.g. doxycycline, minocycline, clindamycin, sulfamethoxazole and trimethoprim [Bactrim], tetracycline, erythromycin, azithromycin, or Vibramycin®) - **1 month prior to Visit 1:** Topical prescription retinoids (e.g. Retin-A®, Retin-A Micro®, Renova®, Adapalene, Tazarotene, Avita®, Tazorac®, Avage®, Differin®), azelaic acid, benzoyl peroxide, dapsone, sodium sulfacetamide, Epiduo®, or other similar prescription drug on the face - **6 months prior to Visit 1:** Accutane or other oral retinoid - **2 weeks prior to Visit 1**: Any of the following on the face: • Light therapy • OTC topical medications/products (including antiacne or antibacterial agents, topical anti-inflammatories, topical retinoids, etc.). Sunscreens (SPF) are acceptable. 5. Females who are pregnant, lactating, or planning to become pregnant

	during the study or within 30 days of study completion. (Subject must document her response in either the source documentation or informed consent/assent forms). 6. Subject has a surgery and/or invasive medical procedure planned during the study. 7. Subject has observable suntan, scars, nevi, tattoo, excessive hair (including beard, mustache, or goatee), or other dermal conditions on the face that that could interfere with study evaluations or confound study results, as determined by the PI or designee. 8. Subject is taking medications that would mask an adverse event (AE) or influence the study results, including: - Immunosuppressive drugs and steroidal and/or non-steroidal anti-inflammatory drugs within 3 months before Visit 1 and during the study. - Regular use of antihistamines within 1 month before Visit 1 and during the study. 9. Subject has a history of or a concurrent health condition/situation, which in the opinion of the PI, if medically qualified, or Study Physician, may put the individual at significant risk, confound the study results, or interfere significantly with the individual's participation in the study. 10. Subject is an employee/contractor or immediate family member of the PI, Study Site, or Sponsor. 11. Subjects with clinically significant unstable medical disorders. 12. Subjects who are unwilling or unable to comply with the requirements of the protocol. 13. Subjects with any known allergies or sensitivities to the study acne products. 14. Subjects who are currently under the care of a dermatologist for acne. 15. Subjects who are currently experiencing an acne flare. 16. Subjects who have history of a psychological illness or condition that would interfere with their ability to understand and follow the requirements of the study. 17. Subjects having started hormone replacement therapies (HRT) or hormones for birth control less than 3 months prior to the study entry or who plan on starting, stopping or changing doses of HRT or hormones for birth control during the study.
Endpoints:	Tolerability Endpoint: The tolerability endpoint is the investigator-assessed absence of skin irritation from the facial study acne products at any time during the study. Safety Endpoint: The safety endpoint is the overall incidence of all adverse events reported during the study.

	Primary Efficacy Endpoint: The primary efficacy endpoint is the reduction in causal sebum measurements from the forehead obtained with a sebumeter during the study. Secondary Efficacy Endpoint: The secondary efficacy endpoint is the changes in the facial microbiome induced by 8, 12, and 52 weeks of clascoterone 1% cream application. [redacted]
Measures:	[redacted] Sebumeter measurements: 3 sebumeter measurements will be taken from the forehead 2-4 hours after facial washing at each study visit. Microbiome assessment: Swabbing of the cheek for microbiome analysis will be performed from all subjects at baseline, week 8, week 12, and week 52.
Statistical	Along with descriptive statistics (means, standard deviations and percentages),

Methods:	investigator and subject ordinal nonparametric data will be analyzed using the Wilcoxon signed rank test. Change will be considered significant at a p value less than or equal to 0.05. Numerical acne lesion counts (inflammatory, noninflammatory, and total lesions) and sebumeter measurements will be assessed with a Student's t test again with significance at a p value less than or equal to 0.05.

2. STUDY VISIT SCHEDULE

Procedures	Visit 1 BL	Visits 2-16 Weeks 2-48	Visit 17 Week 52
Informed Consent Procedure	X		
Inclusion/Exclusion Criteria	X		
Brief Medical History and Concomitant Medications Review	X	X	X
Adverse Event Assessment		X	X
[redacted]			
Microbiome Collection	X	Week 8, 12	X
Product Dispensing (as needed)	X	X	X
Subject Diary Assessment and Compliance Check		X	X

Subject Product Accountability and Study Completion			X

3. INTRODUCTION

The etiology of acne is heavily dependent on the production of sebum by the sebaceous glands that results in the growth of the bacteria c. acnes. If no sebum is present, there is no nutritional source for the c. acnes, the bacteria die, and acne resolves. A newly FDA approved acne medication consisting of clascoterone cream 1% is believed to effectively treat acne due to a decrease in sebum production. This mechanism of action has been postulated based on efficacy observed in the phase III trials that lead to its approval. This research aims to demonstrate the effect of clascoterone cream 1% in sebum reduction.

4. STUDY OBJECTIVE

The objectives of this research are as follows:
Primary Efficacy Endpoint: The primary efficacy endpoint is the reduction in causal sebum measurements from the forehead obtained with a sebumeter during the study.

Secondary Efficacy Endpoint: The secondary efficacy endpoint is the changes in the facial microbiome induced by 8, 12, and 52 weeks of clascoterone 1% cream application.

[redacted]

[redacted]

5. STUDY DESIGN OVERVIEW

Female and male subjects will be enrolled in this single site study to evaluate the effect of clascoterone cream [redacted] on facial sebum production and acne. Subjects who sign consent and meet all inclusion criteria and none of the exclusion criteria will be enrolled at the baseline visit. Subjects will use their own approved skin care products unchanged for the duration of the study.

At baseline visit, subjects will receive the study product. [redacted] Three casual sebumeter measurements will be taken from the central forehead 2-4 hours after the subjects washed prior to presenting to the research center.

[redacted]

[redacted]

[redacted]

Microbiome swabbing for analysis by [redacted] will be obtained from all 40 subjects at baseline, week 8, week 12, and week 52.

6. STUDY POPULATION

6.1 POPULATION DESCRIPTION

Healthy female and male subjects 12+ years of age Fitzpatrick skin types I-VI with mild to moderate acne (10-100 total non-inflammatory lesions (open comedones and closed comedones), 10-50 total inflammatory lesions, no cysts, and up to 2 nodules (if deemed appropriate by the PI) on the face.

6.2 POPULATION SIZE

40 subjects

6.3 INCLUSION CRITERIA

The following items represent the inclusion criteria:

1. Males and females 12+ years of age.
2. Subjects with mild to moderate acne.
3. Subjects must possess 10-100 total non-inflammatory lesions (open comedones and closed comedones), 10-50 total inflammatory lesions, no cysts, and up to 2 nodules (if deemed appropriate by the PI) on the face.
4. Subjects with all Fitzpatrick skin types I-VI.
5. Subjects who agree to use only the study products for acne treatment. No other medicated cleansers or moisturizers or acne treatments of any kind are allowed.
6. Subjects agree not to introduce any new colored cosmetics or skin care products while participating in the study (lipsticks, eye shadows, facial foundations, blush, powder, cleansers, moisturizers).
7. Subjects agree to arrive at all visits with a clean face, having washed his/her face and removed all facial and eye makeup products within 2 hours to 4 hours prior to the visit and is not to use/apply any topical facial product(s) until the visit is completed.
8. No known medical conditions that, in the investigator's opinion, may interfere with study participation.

9. Women of childbearing potential must be willing to use a form of birth control during the study. For the purpose of this study, the following are considered acceptable methods of birth control: oral contraceptives, Norplant®, Depo-Provera®, double barrier methods (e.g., condom and spermicide) and abstinence.
10. Subjects are dependable and able to follow directions and willing to comply with the schedule of visits.
11. Subjects in generally good physical and mental health.
12. Able to read, write, speak, and understand English
13. Individual (and/or his/her legally acceptable representative, as applicable) has signed the Consent for Photograph Release and ICD (and/or Assent Document, as applicable) including Health Insurance Portability and Accountability Act (HIPAA) disclosure.
14. Subject must avoid sun exposure, or use sunscreen if sun exposure is unavoidable.
15. Subject must avoid professional or facial spa procedures during the study.

6.4 EXCLUSION CRITERIA

The following items represent the exclusion criteria:

1. Any dermatological disorder, which in the investigator's opinion, may interfere with the accurate evaluation of the subject's skin characteristics, except for the study condition of acne.
2. Subjects who are not willing to use the assigned study product to their face as instructed.
3. Subjects who have acne nodules/cysts representative of severe acne.
4. Subjects who are currently using, planning to use during the study or has used any of the following in the specified time range (based on subject report):
    a. **1 month prior to Visit 1**: Prescription (oral or topically applied on the face) antibiotics, inhaled steroids (except those prescribed for allergies), or hormones (pre- or post-menopausal hormone-replacement therapy; insulin, etc.), or other medications that could make skin more sensitive or have an effect on the skin, as determined by the PI or designee. Oral contraceptives are acceptable.
    b. **1 month prior to Visit 1:** Prescription medication for acne (e.g. doxycycline, minocycline, clindamycin, sulfamethoxazole and trimethoprim [Bactrim], tetracycline, erythromycin, azithromycin, or Vibramycin®)
    c. **1 month prior to Visit 1:** Topical prescription retinoids (e.g. Retin-A®, Retin-A Micro®, Renova®, Adapalene, Tazarotene, Avita®, Tazorac®, Avage®, Differin®), azelaic acid, benzoyl peroxide, dapsone, sodium sulfacetamide, Epiduo®, or other similar prescription drug on the face
    d. **6 months prior to Visit 1:** Accutane or other oral retinoid
    e. **2 weeks prior to Visit 1**: Any of the following on the face:
        i. • Light therapy
        ii. • OTC topical medications/products (including antiacne or

antibacterial agents, topical anti-inflammatories, topical retinoids, etc.). Sunscreens (SPF) are acceptable.

5. Females who are pregnant, lactating, or planning to become pregnant during the study or within 30 days of study completion. (Subject must document her response in either the source documentation or informed consent/assent forms).
6. Subject has a surgery and/or invasive medical procedure planned during the study.
7. Subject has observable suntan, scars, nevi, tattoo, excessive hair (including beard, mustache, or goatee), or other dermal conditions on the face that that could interfere with study evaluations or confound study results, as determined by the PI or designee.
8. Subject is taking medications that would mask an adverse event (AE) or influence the study results, including:
    a. Immunosuppressive drugs and steroidal and/or non-steroidal anti-inflammatory drugs within 3 months before Visit 1 and during the study.
    b. Regular use of antihistamines within 1 month before Visit 1 and during the study.
9. Subject has a history of or a concurrent health condition/situation, which in the opinion of the PI, if medically qualified, or Study Physician, may put the individual at significant risk, confound the study results, or interfere significantly with the individual's participation in the study.
10. Subject is an employee/contractor or immediate family member of the PI, Study Site, or Sponsor.
11. Subjects with clinically significant unstable medical disorders.
12. Subjects who are unwilling or unable to comply with the requirements of the protocol.
13. Subjects with any known allergies or sensitivities to the study acne products.
14. Subjects who are currently under the care of a dermatologist for acne.
15. Subjects who are currently experiencing an acne flare.
16. Subjects who have history of a psychological illness or condition that would interfere with their ability to understand and follow the requirements of the study.
17. Subjects having started hormone replacement therapies (HRT) or hormones for birth control less than 3 months prior to the study entry or who plan on starting, stopping or changing doses of HRT or hormones for birth control during the study.

6.5 CONCOMITANT MEDICATIONS

All oral prescription medications should remain unchanged during the study. No topical medications of any kind can be used on the face. Subjects must use their own self-selected skin care products during the study that they have used without problems for the past 30 days.

7. CONDUCT OF STUDY: METHODS AND PROCEDURES

7.1 ENROLLMENT

7.1.1 INFORMED CONSENT

A signed informed consent form must be obtained from each subject prior to performing any study procedures. No study related procedures or activities will be performed until each subject is fully informed and the consent form is signed and dated.

7.1.2 DERMATOLOGICAL EXAMINATION

A dermatological examination will be performed.

7.1.3 STUDY PROCEDURES

The subjects will be screened for the inclusion and exclusion criteria prior to study enrollment. Only subjects who meet the requirements, have signed an informed consent, and have given a medical history will be entered into the study. All other subjects will be considered screening failures.

7.1.4 STUDY MATERIAL ADMINISTRATION

All subjects will use clascoterone cream 1% to the face twice daily.

7.1.5 SCREENING PROCEDURES

Potential volunteers will be enrolled based on their ability to meet the inclusion/exclusion criteria required for study enrollment.

7.2 STUDY CONDUCT PROCEDURES

7.2.1 BASELINE

Female and male subjects will be enrolled in this single site study to evaluate the effect of closcoterone cream [redacted] on facial sebum production and acne. Subjects who sign consent and meet all inclusion criteria and none of the exclusion criteria will be enrolled at the baseline visit. Subjects will use their own approved skin care products unchanged for the duration of the study.

At baseline visit, subjects will receive the study product. The dermatologist investigator will assess facial appearance in terms of oily appearance, pore size, and facial shine. [redacted] Three casual sebumeter measurements will be taken from the central forehead 2-4 hours

after the subjects washed prior to presenting to the research center. A microbiome sample will be taken from the cheek.

[redacted]

7.2.2 WEEK 2, WEEK 4, WEEK 6, WEEK 8, WEEK 10, WEEK 12, WEEK 16, WEEK 20, WEEK 24, WEEK 28, WEEK 32, WEEK 36, WEEK 40, WEEK 44, WEEK 48, WEEK 52

Subjects will return to the research center at Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52 for the same assessments as performed at baseline. Old study product and diaries will be collected and new diaires and study product dispensed as needed at each visit. Subjects will continue participation for 52 weeks, at which time their study participation will be completed.

Microbiome sampling will occur at weeks 8, 12, and 52.

8. EFFICACY MEASURES

8.1 STUDY MEASURES

[redacted]

[redacted]

[redacted]

Sebumeter measurements: 3 sebumeter measurements will be taken from the forehead 2-4 hours after facial washing at each study visit.

Microbiome assessment: Swabbing of the cheek for microbiome analysis will be performed from all subjects at baseline, week 8, week 12, and week 52.

8.2 SUBJECT COMPLIANCE

Compliance will be determined from the diary sheets. Subjects will record product application and any comments on the provided weekly diary. Diary sheets will remain at the study center as part of the source documentation records.

8.3 NONCOMPLIANT SUBJECTS

Subjects who are found to be noncompliance will be queried as to the reason for their noncompliance. If noncompliance results from study product problems, a full interview will be conducted by the investigator to determine the nature and severity of the problem and an adverse event will be recorded. Subjects who are noncompliant will be released from their study participation and their last visit will be carried forward in the data analysis.

9. FINAL SUBJECT STATUS

A study termination form will be completed for each study subject who receives study product. This includes subjects who completed the study or who withdrew or were withdrawn from study.

9.1 COMPLETED, DISCONTINUED OR INCOMPLETE SUBJECTS

A completed subject is a subject who has satisfied all study entry criteria and completed the 52-week study. For any subject who has started study and terminates the study prematurely, every effort will be made to obtain final evaluations of clinical status. Reasonable effort will be made to contact any subject lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data and clinical supplies. The investigator will choose the description that best describes the status of the subject at termination.

1. Subject completed the 52-week study period

OR INCOMPLETE/DISCONTINUED DUE TO:

2. Contact dermatitis
3. Adverse experience
4. Serious adverse experience
5. Pregnancy
6. Protocol violation
7. Subject withdrew consent
8. Subject lost to follow-up
9. Other

10. STUDY PRODUCTS & ADMINISTRATION

10.1 FORMULATIONS

The active study product will consist of the currently market prescription drug for acne clascoterone cream 1%.

10.2 PRECAUTIONS

Study products should be used in their intended fashion and not orally consumed or placed in the eyes.

10.3 STUDY PRODUCT ADMINISTRATION

The subjects will apply the clascoterone cream 1% twice daily.

10.4 PACKAGING, LABELING, DISTRIBUTION

Study products will be dispensed in the packaging provided by the sponsor.

10.5 STORAGE AND ACCOUNTABILITY OF STUDY PRODUCT

The study product will be stored at room temperature in a locked, limited access area at the study site. Access to the study product will be limited to the investigator and staff members designated to dispense study medication. A study product log will be used to record the dispensation and return of all study product. The subject number/initials, and the initials and date of the person dispensing and receiving the returned study product will be documented on this form.

10.6 CODE DISCLOSURE

All subjects will receive the same study product and no code will be maintained.

11. ADVERSE EVENTS

11.1 ADVERSE REACTIONS PREVIOUSLY REPORTED

The study product has been reported to rarely produce skin irritation.

11.2 ADVERSE EXPERIENCES

An adverse experience is defined as any untoward medical occurrence (sign, symptom or laboratory finding), regardless of severity and whether or not attributed to the study product.

The investigator/coordinator will report all adverse experiences (AEs) that occur throughout the study. All AEs will be recorded in the appropriate AE log. The report will include: date of onset, a description of the AE, severity, seriousness, action taken, relationship to the study drug, outcome of the event, and date of resolution.

11.2.1 ASSESSMENT OF SEVERITY

The intensity or severity of an AE is characterized as:
Mild: AE which is easily tolerated.
Moderate: AE sufficiently discomforting to interfere with daily activity.
Severe: AE which prevents normal daily activities.

Subjects who are withdrawn from the study due to any AE will be followed by the investigator until the outcome is determined. The investigator will summarize and document all information relating to the AE and follow up.

11.2.2 RELATIONSHIP TO STUDY PRODUCT

The relationship is characterized as:

Not Related - applies to any adverse experience that is clearly not related to use of the study product.
Possible - means the association of the adverse experience with the study product is unknown; however, a relationship between study product and experience cannot be ruled out.
Probable - there is a reasonable temporal relationship between the use of the study product and the adverse experience. Based upon the investigator's clinical experience, the association of the event with the study product seems likely.
Definite - The AE occurs following the application of the study product and it cannot be reasonably explained by any other known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. It disappears or decreases upon discontinuation of the study product and reappears on a re-challenge of the study product. This is necessary to evaluate allergic or irritant contact dermatitis.

11.3 SERIOUS ADVERSE EVENTS

Definition: An SAE is defined as any adverse experience occurring that results in any of the following outcomes:

1. death
2. immediately life-threatening illness
3. hospitalization (> 24 hours) or prolongation of existing hospitalization
4. a persistent or significant disability
5. a congenital anomaly/birth defect
6. "other" important medical event

These are not anticipated, however, should an SAE occur, the primary investigator ([redacted] will immediately notify the sponsor.

12. STATISTICAL METHODS

Along with descriptive statistics (means, standard deviations and percentages), investigator and subject ordinal nonparametric data will be analyzed using the Wilcoxon signed rank test. Change will be considered significant at a p value less than or equal to 0.05. [redacted] sebumeter measurements will be assessed with a Student's t test again with significance at a p value less than or equal to 0.05.

12.1 SAMPLE SIZE RATIONALE

A sample size of 40 study subjects was chosen by the study sponsor.

12.2 SIGNIFICANCE LEVEL

Significance is defined at the $p<0.05$ level based on a two-sided test.

12.3 DROP-OUT (PRODUCT TOLERABILITY) ASSESSMENT

Subjects who discontinue will be queried as to any side effects experienced by the study products.

12.4 SAFETY ASSESSMENT

Incidence of all adverse events reported during the study will be summarized. Tabulated summaries will include adverse events grouped by relation to study product.

12.5 ENDPOINTS

12.5.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the reduction in causal sebum measurements from the forehead obtained with a sebumeter during the study.

12.5.2 SECONDARY EFFICACY ENDPOINT

The secondary efficacy endpoint is the changes in the facial microbiome induced by 8, 12, and 52 weeks of clascoterone 1% cream application

[redacted]

[redacted]

[redacted]

12.5.6 SAFETY ENDPOINT

The safety endpoint is the overall incidence of all adverse events reported during the study.

13. ETHICS

13.1 INFORMED CONSENT

The principles of Informed Consent, according to FDA Regulations and ICH step 5 guidelines on GCPs, will be followed.

Subjects must provide written informed consent prior to any study procedures being completed. Each subject's signed informed consent must be kept on file by the Investigator for Regulatory Authorities' inspection at any time. A copy of the signed and dated consent form will be given to the subject.

13.2 INSTITUTIONAL REVIEW BOARD (IRB)

The study will be submitted to an IRB selected by Dermatology Consulting Services for approval to ensure the safety of the human subjects enrolled in the study.

13.3 SUBJECT CONFIDENTIALITY

All participants are concerned for the individual subject's privacy and, therefore, all subject data will be identified only by a subject identification number and subject initials. However, 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 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, laboratory test result reports to verify transcription accuracy, 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 subject must be informed that his/her medical chart may be reviewed by the sponsor, the Sponsor's authorized representative, or a representative of the FDA. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

14. DOCUMENTATION

14.1 SITE DOCUMENTS REQUIRED FOR INITIATION

Prior to the initiation of the study, the following items must be received:

a) Sponsor approval of study
b) Current curriculum vitae of the Principal Investigator
c) Copy of Principal Investigator's Medical license
d) A signed copy of the protocol Investigator's Agreement page
e) Original Non-Disclosure Agreement
f) Signed Budget Agreement

14.2 STUDY DOCUMENTS SUPPLIED BY THE SPONSOR

Dermatology Consulting Services will provide all study documents.

14.3 MAINTENANCE AND RETENTION OF RECORDS

The study will be conducted according to Good Clinical Practices as outlined in ICH step 5 guidelines by the Food and Drug Administration. 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 with limited access. Regulations require retention for a period of at least two years after last

marketing approval and notification from the sponsor. These regulatory documents should be retained for a longer period if required by local regulatory requirements.

Archiving of data - Copies of all pertinent records will be retained by the investigator for at least two years following final approval of the drug and/or notification from the sponsor. These records include documents pertaining to the receipt and return of drug supplies, IRB, Informed Consent, as well as final signed case report forms. No documents shall be transferred from the site or destroyed without first notifying the sponsor. The sponsor will archive the data for the lifetime of the product.

14.3.1 CASE REPORT FORMS (CRF)

CRFs for individual subjects will be provided and completed by Dermatology Consulting Services, as appropriate. CRFs must be legible and complete.

A CRF must be completed and signed by the investigator for each subject enrolled, including those removed from the study for any reason. The reason for removal must be noted on the study conclusion CRF by the investigator for each subject. CRFs must be kept current to reflect the subject's status at each phase during the course of the study. Subjects are not to be identified on CRFs by name; appropriately coded identification and the subject's initials must be used. The investigator must keep a separate log of the subject's names and addresses.

The following documents will be maintained by the research site:

1. Subject Screening Log: This log will reflect the reason any subject screened for the study was found to be ineligible.
2. Study Personnel Signature Log: This log will contain all site personnel along with their responsibilities and signatures. This log will be maintained at the site throughout the study.
3. Monitoring Log: This log will contain the date and purpose of all monitoring visits by the Sponsor.
4. Enrollment Log: This log will contain subject initials and start and end dates for all subjects enrolled.
5. Product Inventory / Packing Slip Log: This log will reflect the total amount of study product shipped to the site and received and signed for by the Investigator.
6. Product Accountability Log: This log will reflect the total amount of study product dispensed to and returned by each subject.

14.3.2 MONITORING

The study will be monitored by a Sponsor appointed representative, if desired.

14.4 PROTOCOL MODIFICATION

The procedures defined in the protocol and in the CRF will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no deviations from the protocol may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have approval in writing from the Sponsor and the IRB prior to implementation.

14.5 AUDITS/INSPECTIONS

During the course of the study and/or after it has been completed, one or more site visits may be undertaken by auditors as authorized representatives of the Sponsor.

15. USE OF INFORMATION AND PUBLICATION

15.1 CONFIDENTIAL INFORMATION

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, the clinical protocol, case report forms, and other scientific data. Any data collected during the study is considered confidential. This confidential information shall remain the sole property of the Sponsor, shall not be disclosed to others without written consent of the Sponsor, and shall not be used except in the performance of the study.

The information developed during the conduct of this clinical study is also considered confidential and will be used by the Sponsor in connection with the development of the study product. The information may be disclosed as deemed necessary by 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 this study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

Should the investigator wish to publish the results of this study, the investigator agrees to provide the Sponsor with a manuscript for review 60 (sixty) days prior to submission for publication. The Sponsor retains the right to delete from the manuscript confidential information and to prevent publication or modify its timing.

In the event the Sponsor chooses to publish the data from this study a copy will be provided to the investigator at least 30 days prior to the expected date of submission to the intended publisher.

INVESTIGATOR'S AGREEMENT

I have carefully read 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, Good Clinical Practices, and local regulatory guidelines, and will attempt to complete the study within the time designated. I will provide copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted 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 study product 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) in accordance with FDA regulations.

[redacted]

APPENDIX I: CASE REPORT FORMS

The following documents are attached:

1. Screening Questionnaire
2. Inclusion/Exclusion Criteria
[redacted]
5. Sponsor Questionnaire
6. Sebumeter Measurements
7. Adverse Event Assessment
8. Study Termination
9. Informed Consent Form (as a separate file)
10. Subject Diary (as a separate file)

[redacted]

Dermatology Consulting Services, PLLC
Protocol Number: DCS-67-22

SCREENING QUESTIONNAIRE

DATE_____

NAME_____
LAST FIRST MIDDLE INITIAL

DATE OF BIRTH_____ AGE_____

SOCIAL SECURITY_____-_____-_____

GENDER AT BIRTH_____ RACE_____

STREET ADDRESS_____

CITY_____ STATE_____ ZIP_____

E-MAIL_____

CELL PHONE ( )_____-_____ CELL PHONE CARRIER_____

EMERGENCY CONTACT
NAME_____ RELATIONSHIP_____

EMERGENCY CONTACT
CELL PHONE ( )_____-_____

I understand federal law requires any person who receives more than $600 in a calendar year from our office must be issued a 1099 tax form. I understand I must provide my social security number for this reason.

SIGNATURE_____DATE_____

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

1. Males and females 12+ years of age.
2. Subjects with mild to moderate acne.
3. Subjects must possess 10-100 total non-inflammatory lesions (open comedones and closed comedones), 10-50 total inflammatory lesions, no cysts, and up to 2 nodules (if deemed appropriate by the PI) on the face.
4. Subjects with all Fitzpatrick skin types I-VI.
5. Subjects who agree to use only the study products for acne treatment. No other medicated cleansers or moisturizers or acne treatments of any kind are allowed.
6. Subjects agree not to introduce any new colored cosmetics or skin care products while participating in the study (lipsticks, eye shadows, facial foundations, blush, powder, cleansers, moisturizers).
7. Subjects agree to arrive at all visits with a clean face, having washed his/her face and removed all facial and eye makeup products within 2 hours to 4 hours prior to the visit and is not to use/apply any topical facial product(s) until the visit is completed.
8. No known medical conditions that, in the investigator's opinion, may interfere with study participation.
9. Women of childbearing potential must be willing to use a form of birth control during the study. For the purpose of this study, the following are considered acceptable methods of birth control: oral contraceptives, Norplant®, Depo-Provera®, double barrier methods (e.g., condom and spermicide) and abstinence.
10. Subjects are dependable and able to follow directions and willing to comply with the schedule of visits.
11. Subjects in generally good physical and mental health.
12. Able to read, write, speak, and understand English
13. Individual (and/or his/her legally acceptable representative, as applicable) has signed the Consent for Photograph Release and ICD (and/or Assent Document, as applicable) including Health Insurance Portability and Accountability Act (HIPAA) disclosure.
14. Subject must avoid sun exposure, or use sunscreen if sun exposure is unavoidable.
15. Subject must avoid professional or facial spa procedures during the study.

Exclusion Criteria:

1. Any dermatological disorder, which in the investigator's opinion, may interfere with the accurate evaluation of the subject's skin characteristics, except for the study condition of acne.
2. Subjects who are not willing to use the assigned study product to their face as instructed.
3. Subjects who have acne nodules/cysts representative of severe acne.
4. Subjects who are currently using, planning to use during the study or has used any of the following in the specified time range (based on subject report):
    a. **1 month prior to Visit 1**: Prescription (oral or topically applied on the face) antibiotics, inhaled steroids (except those prescribed for allergies), or

hormones (pre- or post-menopausal hormone-replacement therapy; insulin, etc.), or other medications that could make skin more sensitive or have an effect on the skin, as determined by the PI or designee. Oral contraceptives are acceptable.

b. **1 month prior to Visit 1:** Prescription medication for acne (e.g. doxycycline, minocycline, clindamycin, sulfamethoxazole and trimethoprim [Bactrim], tetracycline, erythromycin, azithromycin, or Vibramycin®)

c. **1 month prior to Visit 1:** Topical prescription retinoids (e.g. Retin-A®, Retin-A Micro®, Renova®, Adapalene, Tazarotene, Avita®, Tazorac®, Avage®, Differin®), azelaic acid, benzoyl peroxide, dapsone, sodium sulfacetamide, Epiduo®, or other similar prescription drug on the face

d. **6 months prior to Visit 1:** Accutane or other oral retinoid

e. **2 weeks prior to Visit 1**: Any of the following on the face:

i. Light therapy

ii. OTC topical medications/products (including antiacne or antibacterial agents, topical anti-inflammatories, topical retinoids, etc.). Sunscreens (SPF) are acceptable.

5. Females who are pregnant, lactating, or planning to become pregnant during the study or within 30 days of study completion. (Subject must document her response in either the source documentation or informed consent/assent forms).
6. Subject has a surgery and/or invasive medical procedure planned during the study.
7. Subject has observable suntan, scars, nevi, tattoo, excessive hair (including beard, mustache, or goatee), or other dermal conditions on the face that that could interfere with study evaluations or confound study results, as determined by the PI or designee.
8. Subject is taking medications that would mask an adverse event (AE) or influence the study results, including:
    a. Immunosuppressive drugs and steroidal and/or non-steroidal anti-inflammatory drugs within 3 months before Visit 1 and during the study.
    b. Regular use of antihistamines within 1 month before Visit 1 and during the study.
9. Subject has a history of or a concurrent health condition/situation, which in the opinion of the PI, if medically qualified, or Study Physician, may put the individual at significant risk, confound the study results, or interfere significantly with the individual's participation in the study.
10. Subject is an employee/contractor or immediate family member of the PI, Study Site, or Sponsor.
11. Subjects with clinically significant unstable medical disorders.

12. Subjects who are unwilling or unable to comply with the requirements of the protocol.
13. Subjects with any known allergies or sensitivities to the study acne products.
14. Subjects who are currently under the care of a dermatologist for acne.
15. Subjects who are currently experiencing an acne flare.
16. Subjects who have history of a psychological illness or condition that would interfere with their ability to understand and follow the requirements of the study.
17. Subjects having started hormone replacement therapies (HRT) or hormones for birth control less than 3 months prior to the study entry or who plan on starting, stopping or changing doses of HRT or hormones for birth control during the study.

All inclusion criteria must be met and none of the exclusion criteria. Circle any inclusion criteria that are not met and any exclusion criteria that are met and declare the subject a screening failure.

[redacted]

[redacted]

TIMEPOINT	IGA
Baseline	
Week 2	
Week 4	
Week 6	
Week 8	
Week 10	
Week 12	
Week 16	
Week 20	
Week 24	
Week 28	
Week 32	
Week 36	
Week 40	
Week 44	
Week 48	
Week 52	

[redacted]

[redacted]

TIMEPOINT	PAPULES	PUSTULES	CLOSED COMEDONES	OPEN COMEDONES
Baseline				
Week 2				
Week 4				
Week 6				
Week 8				
Week 10				
Week 12				
Week 16				
Week 20				
Week 24				
Week 28				
Week 32				
Week 36				
Week 40				
Week 44				
Week 48				
Week 52				

[redacted]

TIMEPOINT	Oily Appearance	Pore Size	Facial Shine
Baseline	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 2	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 6	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 8	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 10	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 12	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 16	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 20	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 24	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 28	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 32	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 36	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 40	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 44	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 48	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 52	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4

[redacted]

[redacted]T

TIMEPOINT	Peeling	Dryness	Redness	Swelling
Baseline	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 2	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 6	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 8	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 10	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 12	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 16	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 20	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 24	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 28	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 32	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 36	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 40	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 44	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 48	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 52	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4

[redacted]

[redacted]

TIMEPOINT	Stinging	Burning	Itching
Baseline	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 2	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 6	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 8	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 10	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 12	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 16	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 20	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 24	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 28	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 32	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 36	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 40	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 44	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 48	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Week 52	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4

SEBUMETER MEASUREMENTS
All measurements will be taken 2-4 hours after facial washing.

TIMEPOINT	Sebum Reading 1 (left forehead)	Sebum Reading 2 (middle forehead)	Sebum Reading 3 (right forehead)
Baseline			
Week 2			
Week 4			
Week 6			
Week 8			
Week 10			
Week 12			
Week 16			
Week 20			
Week 24			
Week 28			
Week 32			
Week 36			
Week 40			
Week 44			
Week 48			
Week 52			

ADVERSE EVENT

Did the subject experience any adverse event? Yes or No
*If yes, list below:

Adverse Event	1	2
Start Date mm/dd/yy		
Stop Date mm/dd/yy		
Ongoing*		
Frequency[1]		
Severity[2]		
Relation to Study Med[3]		
Action Taken[4]		
Outcome[5]		
Serious (Y/N)		

[1]Frequency
1=Continuous
2=Intermittent
3=Isolated

[2]Severity
1=Mild
2=Moderate
3=Severe

[3]Relation to Study Med
1=Not related
2=Possible
3=Probable
4=Definite

[4]Action Taken (insert all codes that apply)
1=None
2=Study drug discontinued
3=Non-drug therapy
4=New OTC or R_x drug added

[5]Outcome
1=Resolved
2=Improved
3=Stabilized
4=Ongoing
5=Worsened
6=Lost to follow-up

*Check only if the adverse event is ongoing when subject completes/exits the study.

**Refer to the protocol for definitions of severity and relationship to study product.

Final Subject Status

☐ **The subject completed the study.**

Date Completed: ☐☐☐ ☐☐ ☐☐
Month *Day* *Year*

☐ **The subject discontinued the study prematurely due to the following ONE reason:**

Date Discontinued: ☐☐☐ ☐☐ ☐☐
Month *Day* *Year*

☐ Adverse event, including intercurrent illness, which required study discontinuation (specify) _____

☐ Protocol violation (specify) _____

☐ Lost to follow-up

☐ Subject decision/withdrawal of consent

☐ Other (specify) _____

Investigator's Statement:

I have reviewed all pages of this case report form. To the best of my knowledge, the information recorded on the case report form is a complete and accurate record of this subject's treatment course during the study.

Signature *Printed Name*

Date Signed: ☐☐☐ ☐☐ ☐☐
Month *Day* *Year*