Official title: A Clinical Study to Assess the Skin Barrier Impact of Winlevi

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

NCT number: NCT06415292

Document date: 10-Sep-2023

Sun Pharma Protocol
September 10, 2023

A Clinical Study to Assess the Barrier Impact of Winlevi

STUDY NUMBER	DCS-94-23
INVESTIGATOR	Zoe Diana Draelos, MD
STUDY SITE	Dermatology Consulting Services, PLLC 2444 North Main Street High Point, NC, 27262 [redacted]
[redacted]	[redacted]
SPONSOR	Sun Pharma
INVESTIGATIONAL PRODUCTS	Winlevi
SPONSOR PRIMARY CONTACT	Kizito Kyerematenng [redacted]
STUDY DESIGN	Split Face
VERSION NUMBER	1

PROTOCOL NUMBER: DCS-94-23

STUDY TITLE: A Clinical Study to Assess the Skin Barrier Impact of Winlevi

PROTOCOL DATE: September 10, 2023

The signatures below indicate this document represents the final and accepted protocol.

1. PROTOCOL SYNOPSIS

Title of Study:	A Clinical Study to Assess the Skin Barrier Impact of Winlevi
Study Period:	2 weeks
Test Products:	Winlevi Apply twice daily to entire randomized side of face (product applied to randomized forehead, cheek, and jawline).
Objective:	The objective of this study is to demonstrate the lack of barrier damage induced by Winlevi as measured by corneometry and TEWL.
Design:	Female or male subjects with acne prone skin will be enrolled in this split face single site study evaluating the barrier effects of Winlevi. Subjects who sign consent and meet all inclusion criteria and none of the exclusion criteria will be enrolled at the baseline visit. Subjects will be asked to continue their own, self-selected cleanser and sunscreen throughout the 2-week study with equal application to both sides of the face. The sunscreen and cleanser must have been used for 30 days prior to study enrollment without difficulty. Subjects must apply Winlevi twice daily to the randomized right or left face. Subjects will receive a compliance diary and the blinded study treatment product to be applied to the randomized half face following cleansing, every morning and evening. The assessing dermatologist investigator will be blinded as to which side of the face is receiving the Winlevi treatment. Subjects will be seen at baseline, 24 hours, week 1, and week 2. The dermatologist investigator and subjects will assess tolerability for each side of the face separately at each visit on a 5 point ordinal scale. Noninvasive TEWL and corneometry assessments of both sides of the face will be conducted at baseline, 24 hours, week 1, and week 2. Subjects will complete their study participation at week 2. The compliance diary and all study products will be collected at this time. Women of child bearing potential will be administered a urine pregnancy test at baseline and week 2. *(There is an allowance for an unscheduled visit at any time, if necessary.)*
Study Population:	Healthy female or male subjects 18+ years of age of all Fitzpatrick skin types who self identify as having sensitive acne prone skin.
Number of Subjects:	50 subjects
Inclusion Criteria:	1. Subjects who self identify as having sensitive acne prone skin. 2. Female or male subjects 18+ years of age. 3. Subjects with Fitzpatrick skin types I-VI.

	4. Subject agrees not to introduce any new colored cosmetics (lipsticks, eye shadows, facial foundations, blush, powder) or skin care products during the study. 5. Subjects must be willing to use only a cleanser and sunscreen on the entire face and no other skin care products. 6. Subjects must be willing to use the Winlevi study product to designated half face. No other topical acne treatment products on the entire face for the 2 week duration of the study. 7. Subject has signed an Informed Consent Form in compliance with 21CFR Part 50: "Protection of Human Subjects." 8. Subject is dependable and able to follow directions and is willing to comply with the schedule of visits. 9. Subject is in generally good physical and mental health.
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 conditions associated with sensitive skin. 2. Subjects who are not willing to use only the assigned study product and nothing else one randomized half face, except for cleanser and sunscreen that must remain unchanged during the study. Moisturizers or topical acne treatment products should not be used during the 2 week study period on either side of the face. 3. Subjects who do not agree to refrain from direct sun exposure during the study duration. 4. Subjects who have demonstrated a previous hypersensitivity reaction to any of the ingredients of the study products. 5. Subjects, who are pregnant, breast feeding, or planning a pregnancy. 6. Subjects with clinically significant unstable medical disorders. 7. Subjects who are unwilling or unable to comply with the requirements of the protocol. 8. 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. 9. Subjects who are currently participating in any other clinical study. 10. Subjects with any planned surgeries and/or invasive medical procedures during the course of the study. 11. Subjects who currently or frequently use high doses of anti-inflammatory drugs for a defined medication condition. Aspirin use should not exceed 2 tablets (650 mg) per day. 12. Subjects currently receiving any anticancer, immunosuppressive treatments/ medications (e.g., azathioprine, belimumab, cyclophosphamide, Enbrel, Imuran, Humira, mycophenolate mofetil, methotrexate, prednisone, Remicade, Stelara.), or radiation as determined by the initial paperwork. 13. Subjects with a history of immunosuppression/immune deficiency disorders (including (HIV infection or AIDS) or currently using immunosuppressive medications (e.g., azathioprine, belimumab,

	cyclophosphamide, Enbrel, Imuran, Humira, mycophenolate mofetil, methotrexate, prednisone, Remicade, Stelara) and/or radiation as determined by study documentation.
Endpoints:	Primary Endpoint: The primary endpoint is the change in corneometry reading between the two sides of the face treated with Winlevi versus no treatment. Secondary Endpoints: The secondary endpoint is the change in TEWL reading between the two sides of the face treated with Winlevi versus no treatment.
Measures:	Dermatologist Investigator assessed tolerability parameters: dryness, erythema, scaling, and irritation will be assessed separately for each side of the face. All assessments will be made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, 24 hours, week 1, and week 2. Subject assessed tolerability parameters: dryness, tightness, stinging, itching, and burning will be assessed separately for each side of the face. All assessments will be made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, 24 hours, week 1, and week 2. Noninvasive Biomeasurements: TEWL and corneometry measurements on the right and left cheek will be conducted at baseline, 24 hours, week 1, and week 2.
Statistical Methods:	Along with descriptive statistics (means, standard deviations and percentages), investigator ordinal nonparametric data will be analyzed using Wilcoxon signed rank test and sign test for paired comparison at different time points. The noninvasive parametric data will be analyzed using paired t-test. Change will be considered significant at the alpha level of 0.05.

2. STUDY VISIT SCHEDULE

Procedures	Visit 1	Visit 2	Visit 3	Visit 4
	BL	24 Hours	Week 1	Week 2
Informed Consent Procedure	X			
Inclusion/Exclusion Criteria	X			
Brief Medical History and Concomitant Medications Review	X	X	X	X
Investigator Clinical Grading for Tolerability	X	X	X	X
Subject Clinical Grading for Tolerability	X	X	X	X
Product Dispensing	X			
TEWL (both facial sides)	X	X	X	X
Corneometry (both facial sides)	X	X	X	X
Urine Pregnancy Test (WOCP)	X			X
Adverse Events		X	X	X
Subject Diary Assessment and Compliance Check		X	X	X
Subject Product Accountability and Study Completion				X

3. INTRODUCTION

Acne medications are a common source of facial dryness resulting in skin barrier damage and poor patient compliance. Retinoids and benzoyl peroxide are some of the most frequently prescribed and effective acne medications, however, dryness is an unwanted side effect. A new acne medication, 1% clascoterone, has been placed in a novel vehicle for excellent drug delivery in combination with excellent barrier properties. The barrier properties of 1% clascoterone have never been demonstrated. This study is aimed at better understanding the positive barrier effects of 1% clascoterone.

4. STUDY OBJECTIVE

The objective of this study is to demonstrate the lack of barrier damage induced by Winlevi as measured by corneometry and TEWL.

5. STUDY DESIGN OVERVIEW

Female or male subjects with acne prone skin will be enrolled in this split face single site study evaluating the barrier effects of Winlevi. Subjects who sign consent and meet all inclusion criteria and none of the exclusion criteria will be enrolled at the baseline visit. Subjects will be asked to continue their own, self-selected cleanser and sunscreen throughout the 2-week study with equal application to both sides of the face. The sunscreen and cleanser must have been used for 30 days prior to study enrollment without difficulty. Subjects must apply Winlevi twice daily to the randomized right or left face.

Subjects will receive a compliance diary and the blinded study treatment product to be applied to the randomized half face following cleansing, every morning and evening. The assessing dermatologist investigator will be blinded as to which side of the face is receiving the Winlevi treatment. Subjects will be seen at baseline, 24 hours, week 1, and week 2. The dermatologist investigator and subjects will assess tolerability for each side of the face separately at each visit on a 5 point ordinal scale. Noninvasive TEWL and corneometry assessments of both sides of the face will be conducted at baseline, 24 hours, week 1, and week 2.

Subjects will complete their study participation at week 2. The compliance diary and all study products will be collected at this time. Women of child bearing potential will be administered a urine pregnancy test at baseline and week 2.

6. STUDY POPULATION

6.1 POPULATION DESCRIPTION

Healthy female or male subjects 18+ years of age of all Fitzpatrick skin types who self identify as having sensitive acne prone skin.

6.2 POPULATION SIZE

50 subjects

6.3 INCLUSION CRITERIA

The following items represent the inclusion criteria:

1. Subjects who self identify as having sensitive acne prone skin.
2. Female or male subjects 18+ years of age.
3. Subjects with Fitzpatrick skin types I-VI.
4. Subject agrees not to introduce any new colored cosmetics (lipsticks, eye shadows, facial foundations, blush, powder) or skin care products during the study.
5. Subjects must be willing to use only a cleanser and sunscreen on the entire face and no other skin care products.
6. Subjects must be willing to use the Winlevi study product to designated half face. No other topical acne treatment products on the entire face for the 2 week duration of the study.
7. Subject has signed an Informed Consent Form in compliance with 21CFR Part 50: "Protection of Human Subjects."
8. Subject is dependable and able to follow directions and is willing to comply with the schedule of visits.
9. Subject is in generally good physical and mental health.

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 conditions associated with sensitive skin.
2. Subjects who are not willing to use only the assigned study product and nothing else one randomized half face, except for cleanser and sunscreen that must remain unchanged during the study. Moisturizers or topical acne treatment products should not be used during the 2 week study period on either side of the face.
3. Subjects who do not agree to refrain from direct sun exposure during the study duration.
4. Subjects who have demonstrated a previous hypersensitivity reaction to any of the ingredients of the study products.
5. Subjects, who are pregnant, breast feeding, or planning a pregnancy.
6. Subjects with clinically significant unstable medical disorders.
7. Subjects who are unwilling or unable to comply with the requirements of the protocol.
8. 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.
9. Subjects who are currently participating in any other clinical study.
10. Subjects with any planned surgeries and/or invasive medical procedures during the course of the study.

11. Subjects who currently or frequently use high doses of anti-inflammatory drugs for a defined medication condition. Aspirin use should not exceed 2 tablets (650 mg) per day.
12. Subjects currently receiving any anticancer, immunosuppressive treatments/ medications (e.g., azathioprine, belimumab, cyclophosphamide, Enbrel, Imuran, Humira, mycophenolate mofetil, methotrexate, prednisone, Remicade, Stelara.), or radiation as determined by the initial paperwork.
13. Subjects with a history of immunosuppression/immune deficiency disorders (including (HIV infection or AIDS) or currently using immunosuppressive medications (e.g., azathioprine, belimumab, cyclophosphamide, Enbrel, Imuran, Humira, mycophenolate mofetil, methotrexate, prednisone, Remicade, Stelara) and/or radiation as determined by study documentation.

6.5 CONCOMITANT MEDICATIONS

No topical medications are allowed on the face. No facial skin care products other than sunscreen and cleanser are allowed on the face. The subject must have used the self-selected sunscreen and cleanser for at least 30 days without difficulty.

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 skin examination will be performed to ensure all subject meet inclusion/exclusion criteria.

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

The subjects will use 1% clascoterone as marketed (Winlevi) on one randomized side of the face.

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 or male subjects with acne prone skin will be enrolled in this split face single site study evaluating the barrier effects of Winlevi. Subjects who sign consent and meet all inclusion criteria and none of the exclusion criteria will be enrolled at the baseline visit. Subjects will be asked to continue their own, self-selected cleanser and sunscreen throughout the 2-week study with equal application to both sides of the face. The sunscreen and cleanser must have been used for 30 days prior to study enrollment without difficulty. Subjects must apply Winlevi twice daily to the randomized right or left face. Women of child bearing potential will receive a urine pregnancy test.

Subjects will receive a compliance diary and the blinded study treatment product to be applied to the randomized half face following cleansing, every morning and evening. The assessing dermatologist investigator will be blinded as to which side of the face is receiving the Winlevi treatment. The dermatologist investigator and subjects will assess tolerability for each side of the face separately at each visit on a 5 point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe). Noninvasive TEWL and corneometry assessments of both sides of the face will be conducted. Subjects will be instructed to return to the research facility in 24 hours. A reminder text for compliance will be sent prior to the return visit.

7.2.2 24 HOURS

Subjects will return to the research center in 24 hours. The dermatologist investigator and subjects will assess tolerability for each side of the face separately at each visit on a 5 point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe). Noninvasive TEWL and corneometry assessments of both sides of the face will be conducted. Subjects will be instructed to return to the research facility at week 1. A reminder text for compliance will be sent prior to the return visit.

7.2.3 WEEK 1

Subjects will return to the research center at week 1. The dermatologist investigator and subjects will assess tolerability for each side of the face separately at each visit on a 5 point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe). Noninvasive TEWL and corneometry assessments of both sides of the face will be conducted. Subjects will be

instructed to return to the research facility at week 2. A reminder text for compliance will be sent prior to the return visit.

7.2.4 WEEK 2

Subjects will return to the research center at week 2. The dermatologist investigator and subjects will assess tolerability for each side of the face separately at each visit on a 5 point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe). Noninvasive TEWL and corneometry assessments of both sides of the face will be conducted. Women of child bearing potential will be administered a urine pregnancy test. Subjects will complete their study participation at week 2. The compliance diary and all study products will be collected at this time.

8. EFFICACY MEASURES

8.1 STUDY MEASURES

Dermatologist Investigator assessed tolerability parameters: dryness, erythema, scaling, and irritation will be assessed separately for each side of the face. All assessments will be made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, 24 hours, week 1, and week 2.

Subject assessed tolerability parameters: dryness, tightness, stinging, itching, and burning will be assessed separately for each side of the face. All assessments will be made on a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) at baseline, 24 hours, week 1, and week 2.

Noninvasive Biomeasurements: TEWL and corneometry measurements on the right and left cheek will be conducted at baseline, 24 hours, week 1, and week 2.

8.2 SUBJECT COMPLIANCE

The diary sheets will be used to determine compliance. 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 noncompliant will be queried as to the reason for their noncompliance. If noncompliance results from study product problems, full interviews 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 data carried forward.

9. FINAL SUBJECT STATUS

Study termination forms 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 2-week study. For any subject who has started study and terminates the study prematurely, efforts will be made to obtain final evaluations of clinical status. Reasonable efforts 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 2-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

Subjects will apply Winlevi as currently marketed to one randomized side of the face twice daily

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 study products twice daily to the randomized side of the face. The study products will be labeled left and right to ensure subject compliance. The subjects will receive the following instructions:
Apply twice daily to entire randomized side of face (product applied to randomized forehead, cheek, and jawline).

10.4 PACKAGING, LABELING, DISTRIBUTION

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

10.5 STORAGE AND ACCOUNTABILITY OF STUDY PRODUCT

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

10.6 CODE DISCLOSURE

A randomization code will be maintained indicating which side of the face received the currently marketed Winlevi. An independent blinded dispenser who is not associated with other study activities will randomize the study products and maintain the randomization until data lock occurs.

11. ADVERSE EVENTS

11.1 ADVERSE REACTIONS PREVIOUSLY REPORTED

The study products have 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 will 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 (Zoe Diana Draelos, MD) will accept responsibility to notify the sponsor.

12. STATISTICAL METHODS

Along with descriptive statistics (means, standard deviations and percentages), investigator and subject ordinal nonparametric results will be analyzed using Wilcoxon signed rank test and sign test for paired comparison at different time points. The noninvasive parametric results will be analyzed using paired t-test. Changes will be considered significant at the alpha level of 0.05.

12.1 SAMPLE SIZE RATIONALE

A sample size of 50 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 endpoint is the change in corneometry reading between the side of the face treated with Winlevi versus no treatment.

12.5.2 SECONDARY EFFICACY ENDPOINT

The secondary endpoint is the change in TEWL reading between the side of the face treated with Winlevi versus no treatment.

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. Subject signed informed consents will be kept on file by the Investigator for Regulatory Authorities' inspection at any time. A copy of the signed and dated consent forms will be given to the subject.

13.2 INSTITUTIONAL REVIEW BOARD (IRB)

The study documents 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 results will be identified only by a subject identification number. 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 activities 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.

CRFs 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 CRFs 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 research site will maintain the following documents:

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

14.3.2 MONITORING

The study activities 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 publication timing.

In the event the Sponsor chooses to publish the data from this study, copies 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.

_____ _____

Principal Investigator's Signature Date

APPENDIX I: CASE REPORT FORMS

The following documents are attached:

1. Screening Questionnaire
2. Inclusion/Exclusion Criteria
3. Investigator Questionnaires Tolerability
4. Subject Questionnaires Tolerability
5. Adverse Event Assessment
6. Study Termination
7. Informed Consent Form (as a separate file)
8. Subject Diary (as a separate file)

Dermatology Consulting Services, PLLC
Protocol Number: DCS-94-23

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 to participate in this study.

SIGNATURE_____DATE_____

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

1. Subjects who self identify as having sensitive acne prone skin.
2. Female or male subjects 18+ years of age.
3. Subjects with Fitzpatrick skin types I-VI.
4. Subject agrees not to introduce any new colored cosmetics (lipsticks, eye shadows, facial foundations, blush, powder) or skin care products during the study.
5. Subjects must be willing to use only a cleanser and sunscreen on the entire face and no other skin care products.
6. Subjects must be willing to use the Winlevi study product to designated half face. No other topical acne treatment products on the entire face for the 2 week duration of the study.
7. Subject has signed an Informed Consent Form in compliance with 21CFR Part 50: "Protection of Human Subjects."
8. Subject is dependable and able to follow directions and is willing to comply with the schedule of visits.
9. Subject is in generally good physical and mental health.

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 conditions associated with sensitive skin.
2. Subjects who are not willing to use only the assigned study product and nothing else one randomized half face, except for cleanser and sunscreen that must remain unchanged during the study. Moisturizers or topical acne treatment products should not be used during the 2 week study period on either side of the face.
3. Subjects who do not agree to refrain from direct sun exposure during the study duration.
4. Subjects who have demonstrated a previous hypersensitivity reaction to any of the ingredients of the study products.
5. Subjects, who are pregnant, breast feeding, or planning a pregnancy.
6. Subjects with clinically significant unstable medical disorders.
7. Subjects who are unwilling or unable to comply with the requirements of the protocol.
8. 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.
9. Subjects who are currently participating in any other clinical study.
10. Subjects with any planned surgeries and/or invasive medical procedures during the course of the study.
11. Subjects who currently or frequently use high doses of anti-inflammatory drugs for a defined medication condition. Aspirin use should not exceed 2 tablets (650 mg) per day.
12. Subjects currently receiving any anticancer, immunosuppressive treatments/ medications (e.g., azathioprine, belimumab, cyclophosphamide, Enbrel, Imuran, Humira, mycophenolate mofetil, methotrexate, prednisone, Remicade, Stelara.), or radiation as determined by the initial paperwork.
13. Subjects with a history of immunosuppression/immune deficiency disorders (including (HIV infection or AIDS) or currently using immunosuppressive medications (e.g., azathioprine, belimumab, cyclophosphamide, Enbrel, Imuran, Humira, mycophenolate mofetil, methotrexate, prednisone, Remicade, Stelara) and/or radiation as determined by study documentation.

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.

I certify all inclusion criteria have been met and none of the exclusion criteria have been met.

_____ _____

Zoe Diana Draelos, MD Date

Primary Investigator

INVESTIGATOR TOLERABILITY ASSESSMENT

RIGHT CHEEK

Visits	Baseline	24 Hours	Week 1	Week 2
Dryness	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Erythema	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Scaling	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Irritation	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4

LEFT CHEEK

Visits	Baseline	24 Hours	Week 1	Week 2
Dryness	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Erythema	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Scaling	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Irritation	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4

0=none, 1=minimal, 2=mild, 3=moderate, 4=severe

SUBJECT TOLERABIILTY ASSESSMENT

Please let us know if you are experiencing any of these problems. Please use the following scale: 0=none, 1=minimal, 2=mild, 3=moderate, 4=severe. A lower number means you do not have the problem. Circle your correct response. Please rate both your cheeks separately.

Ask the study staff if you have any questions.

RIGHT CHEEK

Visits	Baseline	24 Hours	Week 1	Week 2
Dryness	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Tightness	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Stinging	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Itching	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Burning	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4

LEFT CHEEK

Visits	Baseline	24 Hours	Week 1	Week 2
Dryness	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Tightness	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Stinging	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Itching	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4
Burning	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4	0..1...2..3..4

NONINVASIVE ASSESSMENTS

	Baseline	24 Hours	Week 1	Week 2
TEWL Right Cheek				
TEWL Left Cheek				
Corneometry Right Cheek				
Corneometry Left Cheek				

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*