Official title: The Efficacy and Safety of Winlevi in Skin of Color Patients With Acne.

Document: Study Protocol

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PILOT STUDY PROTOCOL

Protocol Title	**The efficacy and safety of Winlevi in skin of color patients with acne**
Protocol Number	**WINSCO – 2023**
Amendment 1.0	**07DEC2023**
Protocol Date	**February 6, 2023**
Investigator/Sponsor	

PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the supplements, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH-GCP guidelines.

Investigator

Printed Name	Signature	Date

1 GENERAL INFORMATION

1.1 Introduction

Acne vulgaris is the most common skin disease in patients with skin of color and second most common in Caucasian population[1]. The global prevalence is thought to be as high as 60-80% in individuals 12-25 years of age[1,2]. However, it is not limited to only teenagers but also to adults, especially adult females[3]. The pathogenesis of acne is multifactorial. Genetics may also play a role. The treatment pathway should be directed to different pathogenic factors including, excessive sebum production, hyper keratinization, *P. acnes*, and inflammation[4,5,6,7,8].

Data is limited for skin of color patients in Phase III registration trials. Data is limited because there a few studies that focus on patients with skin of color. Therefore, a unique study dedicated to patients with skin of color in a real-world setting will be welcome to add further evidence to phase III data.

Winlevi is the first topical anti androgen and sebum inhibitor approved for acne vulgaris.[9] However, we do not have any clinical experience with Winlevi in treatment for acne

Therefore ,it is reasonable to study Winlevi to emulate real life practice.

References:

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2. Plewig G, Kligman AM: Acne and rosacea, ed 3. Berlin Springer, 2000.
3. Perkins AC, Maglione J, Hillebrand GG, Miyamoto K, Kimball AB: Acne vulgaris in women, prevalence across the life span. J Womens Health (Larchmt) 2012;21:223-230
4. Williams C, Layton AM: Persistent acne in women: implications for the patient and for therapy. Am J Clin Dermatol 2006;7:218-290
5. Jeremy AH, Holland DB, Roberts SG, Thompson KF, Cunliffe WJ: Inflammatory events are involved in acne lesion initiation. J invest Dermatol 2003;121:20-27
6. Nagy I, Pivarcsi A, Koreck A, Szell M, Urban E, Kemeny L: Distinct strains of *Propioni-bacterium acnes* induce selective human β-defensin-2 and interleukin-8 expression in human keratinocytes through toll-like receptors. J Invest Dermatol 2005;124:931-938
7. Holland C, Mak TN, Zimny-Arndt U, Schmid M, Meyer TF, Jungblut PR, Bruggemann H: Proteomic indentification of secreted proteins of *Propionibacterium acnes*. BMC microbiol 2010;10:230
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9. Winlevi packge insert

1.2 Study Population

Ten (10) subjects with moderate to severe facial acne vulgaris.

2 STUDY OBJECTIVES

The objectives of this study are to observe the efficacy and safety of Winlevi in skin of color patients with acne.

Primary objective: Percent of subjects who are clear or almost clear on IGA scale at week 16.

Secondary objectives:

1. Percent of subjects who are clear or almost clear at weeks [redacted]
2. Percent of total lesion reduction at week [redacted] compared to baseline
3. Percent of inflammatory lesion reduction at week [redacted] compared to baseline
4. Percent of non-inflammatory lesion reduction at week [redacted] compared to baseline.
5. Tolerability measures such as, erythema, scaling, dryness, oiliness, burning/stinging, and pruritus.

3 STUDY DESIGN

This is a single-center, open-label pilot study. All study subjects will receive both Winlevi at baseline. The duration of the study is [redacted] weeks and consists of a Screening, Baseline Visit, and Follow-up Visits at Weeks [redacted] The treatment period is [redacted] weeks and [redacted] weeks of safety follow up totaling to [redacted] weeks.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

i. Outpatient, male or female subjects of any race (Fitzpatrick skin types IV, V, VI), and at least 12 years of age or older. Female subjects of childbearing potential must have a negative urine pregnancy test result at Baseline (test must have a sensitivity of at least 25mIU/ml for human chorionic gonadotropin) and practice a reliable method of contraception throughout the study:

A female is considered of childbearing potential unless she is:

- *postmenopausal for at least 12 months prior to study drug administration;*
- *without a uterus and/or both ovaries; or*
- *has been surgically sterile for at least 6 months prior to study drug administration.*

Reliable methods of contraception are:

- *hormonal methods or intrauterine device in use ≥ 90 days prior to study drug administration;*
- *barrier methods plus spermicide in use at least 14 days prior to study drug administration; or*
- *vasectomized partner (vasectomy must be performed 3 months prior to first study drug administration or in the alternative a zero sperm count will suffice)*

[Exception: Female subjects of childbearing potential who are not sexually active will not be required to practice a reliable method of contraception. These subjects may be enrolled at the Investigator's discretion if they are counseled to remain sexually inactive during the study and understand the possible risks in getting pregnant during the study.]

ii. Facial acne IGA score of 3 or 4.

iii. Able to understand the requirements of the study and sign Informed Consent/HIPAA Authorization forms. Subjects under the legal age of consent in the state where the study is conducted must also have the written, informed consent of a parent or legal guardian.

4.2 Exclusion Criteria

i. Female subjects who are pregnant (positive urine pregnancy test), breast-feeding, or who are of childbearing potential and not practicing a reliable method of birth control.

ii. Allergy or sensitivity to any component of the test medications (Section 5.2).

iii. Subjects who have not complied with the proper wash-out periods for prohibited medications (Supplement I).

iv. Medical condition that, in the opinion of the Investigator, contraindicates the subject's participation in the clinical study.

v. Skin disease/disorder that might interfere with the diagnosis or evaluation of acne vulgaris

vi. Evidence of recent alcohol or drug abuse.

vii. History of poor cooperation, non-compliance with medical treatment, or unreliability.

viii. Exposure to an investigational drug study within 30 days of the Baseline Visit.

4.3 Withdrawal of Subjects

It is the right and duty of the Investigator to discontinue the study participation of a subject when the subject's health or well-being is threatened by continuation in the study. Such subjects should be withdrawn from the study.

The following are circumstances that would result in the subject's discontinuation from the study:

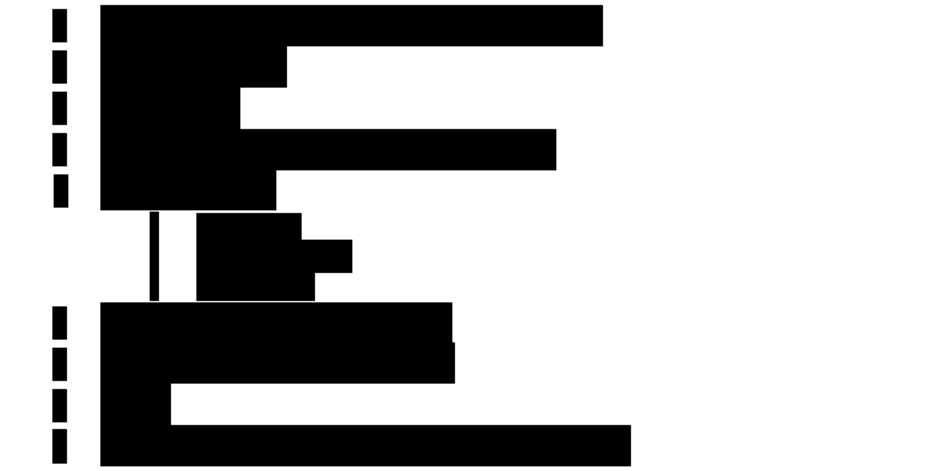
- the subject experiences a serious adverse event rendering them unable to continue study participation;
- the subject is unable to physically or mentally tolerate the use of the test medication;
- an exclusion criterion becomes apparent at any time during the study; or
- the subject voluntarily withdraws.

In the event of premature discontinuation from the study, the Investigator should determine the primary reason for discontinuation. A subject who is withdrawn from the study prior to initiation of treatment may be replaced.

5 TREATMENT OF SUBJECTS AND FOLLOW-UP

5.1 Study Procedures

[redacted]



5.2 Study Treatment

5.2.1 Details of Study Treatment

WINLEVI cream 1% is supplied in [redacted] 60-gram tube

5.2.2 Storage and Handling

WINLEVI (clascoterone) cream contains clascoterone, an androgen receptor inhibitor, in a cream base for topical dermatologic use. WINLEVI cream is a white to almost white cream. Chemically, clascoterone is [redacted] Clascoterone is a white to almost white powder, practically insoluble in water. The compound has the empirical formula [redacted] and molecular weight of [redacted]. The structural formula is shown below. Each gram of WINLEVI cream 1% contains 10 mg of clascoterone in a cream base of [redacted]

5.2.3 Dispensation and Dosage Schedule

Winlevi Cream• Apply a thin layer (approximately 1 gram) to affected area twice daily (morning and evening). Avoid contact with eyes, mouth, and mucous membranes. (2) • Not for ophthalmic, oral or vaginal use. (2)

5.2.4 Treatment Assignment

The study medication will be administered only to eligible subjects as defined by the Study Protocol. All subjects who have signed an ICF will receive a 2-digit subject number, starting at 01. This subject number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number. New subjects will be allotted a new subject number.

5.2.5 Blinding, Packaging, and Labeling

Commercially available and labeled medications will be used. Medications will be dispensed in an open-label fashion.

5.2.6 Supplies and Accountability

The Investigator or pharmacist will inventory and acknowledge receipt of all shipments of study medication. All study medication must be kept in a locked area with access restricted to designated study personnel. The study medication must be stored in accordance with the instructions provided with the shipment. The Investigator or pharmacist will also keep accurate records of the quantities of study medication dispensed and returned by each subject.

5.2.7 Treatment Compliance

Subject compliance to study treatment regimen will be assessed at each visit; study personnel will ask each subject whether they missed any applications of study medication since the previous visit.

5.3 Concomitant Medication/Treatment

Please see Supplement I for a listing of prohibited medications. Necessary therapies that will not interfere with the response to treatment may be provided at the discretion of the Investigator. The use of any concurrent medication, prescription or over-the-counter drug, is to be recorded in the CRF along with the reason the medication was taken.

5.4 Summary of known and potential risks

5.5 Summary of Benefits

There may be certain direct benefits derived from participating in this study. Such benefits include temporary, partial or complete, clearance of your acne lesions; however, it is possible that you receive no benefit. The results of this study may be useful in the development of a new therapy for others with similar conditions to yours.

6 STUDY ASSESSMENTS

6.1 Primary Endpoint

The primary endpoint of this study is the percent of patients who achieve clear or almost clear on IGA at week 16.

6.1.1 Acne IGA

The Investigator will evaluate global acne severity using the following Investigator Global Assessment scale:

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

6.2 Secondary Endpoints

1. Percent of total lesion reduction at week 16 compared to baseline
2. Percent of inflammatory lesion reduction at week 16 compared to baseline
3. Percent of non-inflammatory lesion reduction at week 16 compared to baseline.
4. Tolerability measures such as, erythema, scaling, dryness, oiliness, burning/stinging and pruritus.

6.2.1 Tolerability

The Investigator will grade the ***current*** severity of erythema (disease related and/or related to IP use), dryness, peeling, and oiliness as per the following:

Score	Erythema	Dryness	Peeling	Oiliness
0 = Absent	*No redness*	*None*	*Smooth*	*Normal*
1 = Trace	*Faint red or pink coloration, barely perceptible*	*Barely perceptible dryness by palpation with no accentuation of skin markings, skin desquamation (flakes) or fissure formation*	*Fine peeling, barely perceptible*	*Mild and localized*
2 = Mild	*Light red or pink coloration*	*Easily perceptible dryness by palpation with accentuation of skin markings but no skin desquamation (flakes) or fissure formation*	*Slight peeling*	*Mild and diffuse*
3 = Moderate	*Medium red coloration*	*Easily noted dryness with accentuation of skin markings and skin desquamation (small flakes) but no fissure formation*	*Definitely noticeable peeling*	*Moderate and diffuse*
4 = Severe	*Beet red coloration*	*Easily noted dryness with accentuation of skin markings, skin desquamation (large*	*Extensive peeling*	*Prominent and dense*

flakes) and/or fissure formation

The **Investigator** will **interview the subject** to determine the *current* severity of pruritus and burning/stinging; these symptoms will be graded as per the following:

Score	Description
0 = Absent	*Normal, no discomfort*
1 = Trace	*An awareness, but no discomfort and no intervention required*
2 = Mild	*Noticeable discomfort causing intermittent awareness*
3 = Moderate	*Noticeable discomfort causing continuous awareness*
4 = Marked	*Definite discomfort causing continuous awareness interfering occasionally with normal daily activities*
5 = Severe	*Definite, continuous discomfort interfering with normal daily activities*

6.2.3 Vital Signs

The Investigator will measure vital signs (SBP, DBP, HR, T°) and weight as per his standard of care.

7 ASSESSMENTS OF SAFETY

7.1 Safety Assessments

Throughout the study, subjects will be monitored for signs and symptoms of adverse events. An *adverse event* is any pathological or unintended change in the structure, function or chemistry of the body that occurs during the study, irrespective of causality, including any illness, injury, toxicity, sensitivity, or sudden death. The condition must either not be present pre-study or must worsen in either intensity or frequency during the study.

A *serious adverse event* is any untoward medical occurrence, that, at any dose:

- results in death;
- is life-threatening;
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is an important medical event.

An *unexpected adverse event* is any treatment-related adverse event, which is not identified in nature, severity, or frequency in current literature on the test product.

7.2 Reporting Requirements

7.2.1 Serious and/or Unexpected Adverse Events

Any serious or treatment-related unexpected adverse event occurring in this study must be reported to the IRB within its stipulated reporting timelines.

7.2.2 Adverse Event Reporting

All adverse events must be recorded by the Investigator into the CRF. The Investigator will be required to describe the adverse event, onset and stop date, severity, the course of action taken, if any, as well as any pertinent data necessary to allow a complete evaluation of the adverse event. For serious adverse events, an additional report (SAE report) must be completed.

7.2.3 Follow-up and Final Reports

Subjects who have had a serious adverse event must be followed clinically until all parameters, including laboratory values (if applicable), have either returned to normal or are otherwise explained.

If death was the outcome of the event on the initial SAE Report, a Follow-up/Final Report, including autopsy report, when performed, must be completed.

8 STATISTICS

8.1 Sample Size Justification

A total of 10 subjects will be entered into the study. This is a pilot study and a formal justification for the sample size is not provided. The data from this study will provide important data for determining any trends regarding the safety and efficacy of study medication.

8.2 Analyses

Statistical analyses will be conducted on an intent-to-treat basis (i.e., all enrolled subjects will be included in the analyses). All statistical tests will be two-sided and interpreted at a 5% significance level. Descriptive statistics (i.e., mean, standard deviation, etc.) will be provided for all continuous variables and frequencies for all categorical variables collected in this study. These will be presented by treatment group. Summary tables will be used to present patient population characteristics at Baseline; data from the study questionnaires will be included. The incidence and severity of adverse and/or unexpected events will be tabulated and a complete listing of all reports of adverse and/or unexpected events will be presented.

8.3 Interim Analyses

No interim analyses will be conducted.

9 RESPONSIBILITIES OF THE INVESTIGATOR

9.1 Good Clinical Practice

Investigators must adhere to the procedures outlined in this Study Protocol. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigators and CRO abide by GCP as described in the ICH Guidelines Topic E6: “Guideline for Good Clinical Practice.” Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

9.2 Ethics

The appropriate IRB must review the Study Protocol and the Informed Consent Form prior to initiating the study. Any significant modifications to the IRB-approved protocol or informed consent must be made in consultation with the IRB.

9.3 Confidentiality of Subjects

Any information that identifies subjects with respect to this research study will be kept confidential. However, records identifying the subject may be inspected by representatives of the IRB, the Clinical Research Organization (or its designate) if applicable, and/or the FDA. Subjects’ identity will remain strictly confidential during all record reviews, as well as in any publication that may result from this research. Subjects will be identified by study code only; their names will not be used.

9.4 Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Appropriate discussion of risks and possible benefits of this therapy will be provided to the subjects. Consent forms describing in detail the study interventions/products, study procedures and risks will be given to the subject and written documentation of informed consent is required prior to starting intervention/administration study product. Consent forms will be IRB approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.5 Data Handling and Record Keeping

Investigators must ensure that proper source documentation for all study activities are diligently maintained and securely kept. Investigators will transfer all relevant data from source documents to the Case Report Form as stipulated in this Study Protocol and his/her signature on the Case Report Form guarantees completeness and integrity of these data. Investigators will maintain reliable study device dispensing/dosing records and will store study supplies in a secure, locked location. In addition, Investigators will ensure that all study-related source documentation and Case Report Forms will be maintained for a period of two years after the conclusion of the study.

9.6 Direct Access to Source Data/Documents

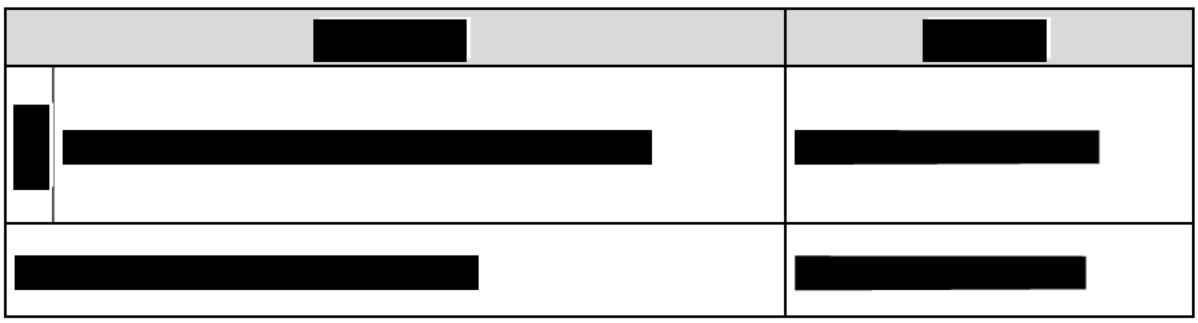
Investigators must ensure that institutional regulations and the Informed Consent Form clearly permit study-related monitoring, audits, IRB review, and regulatory inspections providing direct access to source data and documents.

10 SUPPLEMENTS

I Prohibited Medications / Wash-Out Periods

SUPPLEMENT I
Prohibited Medications / Wash-Out Periods

Use of the following medications (concurrent and contraindicated treatments) are prohibited during the course of the study and appropriate wash-out periods must be respected:



[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Dermatology Life Quality Index (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please circle one response for each question below.

1. Over the last week, how itchy, sore, painful or stinging has your skin been?
    a. Very Much
    b. A Lot
    c. A Little
    d. Not at All

2. Over the last week, how embarrassed or self-conscious have you been because of your skin?
    a. Very Much
    b. A Lot
    c. A Little
    d. Not at All

3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?
    a. Very Much
    b. A Lot
    c. A Little
    d. Not at All
    e. Not Relevant

4. Over the last week, how much has your skin influenced the clothes you wear?
    a. Very Much
    b. A Lot
    c. A Little
    d. Not at All
    e. Not Relevant

5. Over the last week, how much has your skin affected any social or leisure activities?
    a. Very Much
    b. A Lot
    c. A Little
    d. Not at All
    e. Not Relevant

6. Over the last week, how much has your skin made it difficult for you to do any sport?
    a. Very Much
    b. A Lot
    c. A Little
    d. Not at All

e. Not Relevant

7. Over the last week, has your skin prevented you from working or studying?
    a. Yes
    b. No
    c. Not Relevant

        If “No”, over the last week how much has your skin been a problem at work or studying?
        a. A Lot
        b. A Little
        c. Not at All

8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?
    a. Very Much
    b. A Lot
    c. A Little
    d. Not at All
    e. Not Relevant

9. Over the last week, how much has your skin caused any sexual difficulties?
    a. Very Much
    b. A Lot
    c. A Little
    d. Not at All
    e. Not Relevant

10. Over the last week, how much of a problem has the treatment of your skin been, for example by making your home messy, or by taking up time?
    a. Very Much
    b. A Lot
    c. A Little
    d. Not at All
    e. Not Relevant