STUDY PROTOCOL

Protocol Title	**The Use of Onexton in Moderate Acne Vulgaris for Patients with Skin of Color**
Protocol Date	**31JAN2017**
Investigator/Sponsor	**Leon Kircik, MD** **1169 Eastern Parkway, Suite 2310** **Louisville, Kentucky 40217** **USA**

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

LEON KIRCHIC		8/2/17
Printed Name	Signature	Date

1 GENERAL INFORMATION

1.1 Introduction

Acne vulgaris is a chronic disease with devastating sequela of post-inflammatory hyperpigmentation (PIH) in patients with skin of color. The treatment of PIH in acne is complicated and controversial because some treatments such as topical retinoids may cause further PIH due to irritation.
There are several studies evaluating topical retinoids as well as Azelaic acid 15% gel. There is not much information about the effect of benzoyl peroxide and clindamycin combination in acne patients with skin of color except sub-analysis from a community based study with BP 5% and clindamycin combination at AM and a topical retinoid at PM regimen.
Therefore, the use of Onexton Gel as monotherapy in acne patients with only skin of color will be a novel contribution to our knowledge base.

1.2 Study Population

Twenty (20) subjects with skin of color who are 12 years of age or older with moderate facial acne vulgaris and moderate PIH on IGA scale

3 STUDY DESIGN

This is a single-center, open label pilot study. The study is comprised of 5 study visits; Screening, Baseline, and weeks 4, 8, and 16. All subjects will receive Onexton QD at Baseline. We will evaluate Investigator Global Assessment of acne (IGA), total lesion count, inflammatory lesion count, non-inflammatory lesion count, Investigator Global Assessment of PIH and distribution of PIH, adverse events and concomitant medications.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

i. Outpatient, subjects of skin of color, age 12 or older. Female subjects of childbearing potential must have a negative urine pregnancy test result at Baseline 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:
- *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.*

[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 vulgaris in patients with skin of color (Fitzpatrick Type V & VI Supplement VI) characterized by the following:
- IGA Score for acne vulgaris 3
- IGA Score for PIH 3

iii. Able to understand and comply with the requirements of the study and sign Informed Consent/HIPAA Authorization forms.

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/sensitivity to any component of the test treatment

iii. IGA score for acne or 2 (mild) or 4 (severe)

iv. IGA score for PIH or 2 (mild) or 4 (severe)

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

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

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

viii. Evidence of recent alcohol or drug abuse.

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

x. 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 and not continued under a modified regimen.

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

5.1.1 Assessment Schedule

	Screening[0]	Baseline		EOT
	Visit 1 0-28days	Visit 2 Wk 0	Visit 3, 4 Wk 4, 8	Visit 5 Wk 16
ICF/HIPAA ✓	X			
Subject Demographics/Medical Hx ✓	X			
Inclusion/Exclusion Criteria ✓	X	X		
Urine Pregnancy Test [1] ✓	X	X	X	X
Lesion Counts [2] ✓	X	X	X	X
Investigator Global Assessment Acne (IGA) ✓	X	X	X	X
Investigator Global Assessment PIH (IGA) ✓	X	X	X	X
PIH Distribution ✓	X	X	X	X
Subject assessments signs and symptoms stinging/burning and pruritus ✓	X	X	X	X
Signs and Symptoms (Investigator) [3] ✓	X	X	X	X
Study Medication Dispense / Collect ✓		D C	D C	C
Concomitant Medication/Treatment ✓	X	X	X	X
Adverse Events ✓		X	X	X

0 Screening and baseline can be the same day if subject does not need a washout

1 Female subjects of childbearing potential

2 Lesion Counts: papules, pustules, nodules, open/closed comedones

3 Peeling, erythema, dryness, oiliness

5.1.2 Visit 1 & 2 (Screening/Baseline Visit)

- Informed Consent/HIPAA
- Urine Pregnancy Test (if applicable)
- Subject Demographics/Medical History
- Concomitant Medication/Treatment
- Investigator Assessments
  - *IGA acne, IGA PIH, PIH distribution, Lesion Counts, Signs and Symptoms (peeling, erythema, dryness, oiliness)*
- Inclusion/Exclusion Criteria
- Subject Assessments
  - *Signs and Symptoms (burning, pruritus)*
- Dispense study medication

5.1.3 Visits 3, 4, (Week 4, & 8 ± 3 days)

- Urine Pregnancy Test (if applicable)
- Concomitant Medication/Treatment
- Adverse Events

- Subject Assessments
  - *Signs and Symptoms*
- Assess treatment compliance
- Investigator Assessments *IGA acne, IGA PIH, PIH distribution, Lesion Counts, Signs and Symptoms (peeling, erythema, dryness, oiliness)*

5.1.6 Visit 5 (Week 16; ± 5 days)

- Urine pregnancy test if applicable
- Concomitant Medication/Treatment
- Adverse Events
- Investigator Assessments *IGA acne, IGA PIH, PIH distribution, Lesion Counts, Signs and Symptoms (peeling, erythema, dryness, oiliness)*
- Subject Assessments
  - *Signs and Symptoms*
- Collect study medication

5.2 Study Treatment

5.2.1 Details of Study Treatment

Active ingredients of Onexton are clindamycin phosphate of 10mg in 1gm and benzoyl peroxide of 37.5mg in 1gm. Inactive ingredients include water, carbomer, homopolymer type C, propylene glycol, potassium hydroxide. It is dispensed 50gm in one bottle pump.

5.2.2 Dispensation and Dosage Schedule

See supplement II

5.2.3 Treatment Assignment and Subject Numbering

All subjects will receive the study medication. Study medication will be administered only to subjects included in this study following the procedures set out in 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.

5.2.4 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. At study conclusion, all used and unused study medication will be destroyed as per the typical practice of the investigative site.

5.2.5 Treatment Compliance

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

5.3 Concomitant Medication/Treatment

Any 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/treatment is to be recorded in the source.

6 ASSESSMENTS OF EFFICACY

6.1 Primary Efficacy Variable (Co-Primary endpoints will be the percent of subjects achieving clear or almost clear on IGA scale for acne and PIH at week 16.

6.2 Secondary Efficacy Variables: Secondary endpoints will be (1) the percent reduction of inflammatory lesion count at week 16. (2) percent reduction of non-inflammatory lesions at week 16. (3) percent reduction of total lesion count at week 16 (4) the change in PIH distribution at week 16.

6.2.1 Inflammatory Lesion Counts (Papules/Pustules)

The Investigator will count the number of papules/pustules at each study visit using the following guidelines:

- Use only the face in the assessment (the whole face down from the hairline edge to the mandibular line); and
- Count one side of the face and then the other.

6.2.2 Non-Inflammatory Lesion Counts (Open/Closed Comedones)

The Investigator will count the number of open and closed comedones at each study visit using the following guidelines:

- Use only the face in the assessment (the whole face down from the hairline edge to the mandibular line);
- Do not count prominent follicular markings on the nose as open comedones; and
- Count one side of the face and then the other.

6.2.3 Inflammatory Lesion Counts (Nodules)

The Investigator will count the number of nodules at each study visit using the following guidelines:

- Use only the face in the assessment (the whole face down from the hairline edge to the mandibular line); and
- Count one side of the face and then the other.

6.2.4 Investigator Global Assessment for Acne – SUPPLEMENT III

This assessment should be done prior to lesion count

6.2.5 Investigator Global Assessment for PIH – SUPPLEMENT IV

This assessment should be done prior to lesion count and prior to PIH distribution assessment

6.2.6 PIH Distribution Assessment – SUPPLEMENT V

6.2.4 Disease Signs and Symptoms

The Investigator will grade the *current* severity of erythema (disease related and/or related to retinoid 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 flakes) and/or fissure formation*	*Extensive peeling*	*Prominent and dense*

The **Investigator** will **interview the subject** to determine the severity of pruritus and burning *since the last visit*; 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*

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 promptly reported to the IRB as per its reporting guidelines.

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

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 Wash-Out Periods for Prohibited Medications
II Study Treatment Application Procedure
III IGA

SUPPLEMENT I
Wash-Out Periods for Prohibited Medications

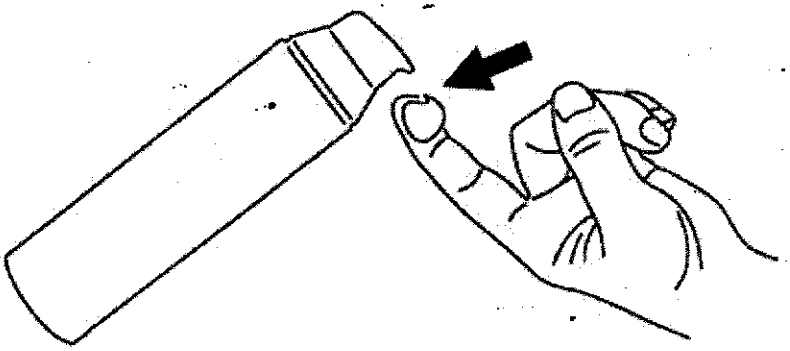
Use of the following medications (concurrent and contraindicated treatments) have either restrictions for usage, or are prohibited during the course of the study and appropriate wash-out periods must be respected:

Medication	**Wash-Out Period/Restrictions**
Topical Medications on Face ▪ *Retinoids* ▪ *Rx Acne Medications (e.g., BPO, antibiotics)* ▪ *OTC Products that contains active ingredients (e.g., BPO washes, BPO lotions, sal acid, etc.)* ▪ *Corticosteroids*	 14 days prior to Visit 1 14 days prior to Visit 1 7 days prior to Visit 1 14 days prior to Visit 1
Systemic Medications ▪ *Antibiotics (indicated for acne vulgaris , no wash out if it is used for sore throat or any other infectious process)* ▪ *Corticosteroids (indicated for acne vulgaris)* ▪ *Antimalarial medications* ▪ *Oral dapsone* ▪ *Retinoids*	 30 days prior to Visit 1 30 days prior to Visit 1 30 days prior to Visit 1 30 days prior to Visit 1 6 months prior to Visit 1
Isotretinoin	6 months
OTC Acne Products without any active ingredients (e.g. apricot scrubs)	1 Day washout prior to Visit 1
Investigational Drugs	30 Day washout prior to Visit 1
Cosmetic / Surgical Procedures complementary to the treatment of facial acne	2 Weeks

SUPPLEMENT II
Study Treatment Application Procedure

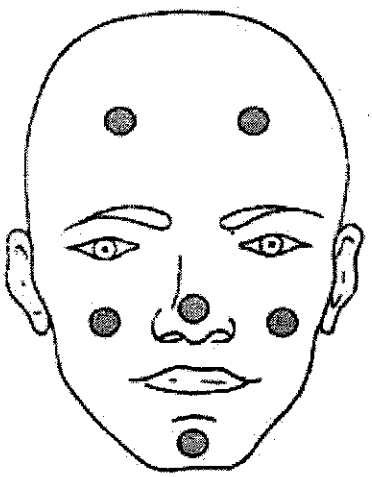
- Use ONEXTON Gel exactly as your doctor tells you to use it.
- Apply ONEXTON Gel to your face 1 time each day.
- Before you apply ONEXTON Gel, wash your face gently with a mild soap, rinse with warm water, and pat your skin dry.
- To apply ONEXTON Gel to your face, use the pump to dispense 1 pea-sized amount of ONEXTON Gel onto your fingertip (See Figure 1). One pea-sized amount of ONEXTON Gel should be enough to cover your entire face.

Figure 1



- Dot the 1 pea-sized amount of ONEXTON Gel onto six areas of your face (chin, left cheek, right cheek, nose, left forehead, right forehead). See Figure 2.

Figure 2



- After applying the ONEXTON Gel this way, spread the gel over your face and gently rub it in. It is important to spread the gel over your whole face.
- Wash your hands with soap and water after applying ONEXTON Gel.
- If your doctor tells you to put ONEXTON Gel on other areas of your skin with acne, be sure to ask how much you should use.
- Do not use more ONEXTON Gel than prescribed.

Supplement III

Investigator Global Assessment for Acne IGA)

The Investigator will evaluate the IGA using the following scale and **before assessing individual lesions counts**:

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*

Supplement IV:

Investigator Global Assessment for PIH

0 = NONE
1 = Slight
2 = mild
3 = moderate
4 = moderately severe
5 = severe
6 = Very severe

Supplement V:
0 = No PIH
1 = 1% - 10% PIH of the face
2 = 11% - 20% PIH of the face
3 = 21%- 30% PIH of the face
4 = 31% - 40% PIH of the face
5 = 41% - 50% PIH of the face
6 = More than 50% PIH of the face

SUPPLEMENT VI

FITZPATRICK SKIN TYPE CLASSIFICATION

Skin Type	Description	Examples
I	Always burns easily and severely (painful burn); tans little or none and peels.	People most often with fair skin, blue eyes and freckles; unexposed skin is pale white.
II	Usually burns easily and severely (painful burn); tans minimally or lightly, also peels.	People most often with fair skin, red or blond hair, hazel or even brown eyes; unexposed skin is pale white.
III	Burns moderately and tans about average.	Normal, average Caucasoid; unexposed skin is white.
IV	Burns minimally, tans easily and above average with each exposure; exhibits IPD (immediate pigment darkening) reaction.	People with white or light brown skin, dark eyes (e.g. Mediterranean, Mongoloids, Oriental, Hispanics, etc.); unexposed skin is white or light brown.
V	Rarely burns; tans easily and substantially; always exhibits IPD reaction.	Brown-skinned persons (e.g. Amerindians, East Indians, Hispanics, etc.); unexposed skin is brown.
VI	Never burns and tans profusely; Exhibits IPD reaction.	Black-skinned persons (e.g. African-Americans, Australian and South Indian Aborigines); unexposed skin is black or dark brown.