

## **STUDY PROTOCOL**

<b>Protocol Title</b>	<b>The Use of Oracea and Epiduo Forte in Severe Acne Patients</b>
<b>Protocol #</b>	<b>ORA-1801</b>
<b>Protocol Date</b>	<b>09JAN2018</b>
<b>Investigator/Sponsor</b>	<b>Leon Kircik, MD 1169 Eastern Parkway, Suite 2310 Louisville, Kentucky 40217 USA</b>

## 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**

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Printed Name

Signature

Date

## **1 GENERAL INFORMATION**

### **1.1 Introduction**

Acne is primarily an inflammatory disease. The combination treatment of Oracea with its anti-inflammatory effect and Epiduo Forte with both anti-inflammatory and anti-comedogenic properties may be the ideal treatment for severe acne avoiding oral or topical antibiotics..

### **1.2 Study Population**

Twenty (20) subjects who are 12 years of age or older with severe acne vulgaris.

## **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 12. All subjects will receive Oracea QD and Epiduo Forte at Baseline. We will evaluate Investigator Global Assessment (IGA), total lesion count, inflammatory lesion count, non-inflammatory lesion count, adverse events and concomitant medications.

## **4 SELECTION AND WITHDRAWAL OF SUBJECTS**

### **4.1 Inclusion Criteria**

- i. Outpatient, male or female subjects of any race, 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  $\geq 90$  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 4
- iii. Minimum of 20 or more inflammatory lesions and 20 or more non-inflammatory lesions and not more than 4 nodules
- iv. 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.

### **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 medication.

- 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 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/ Baseline	Follow-up Visits	
		Visit 1 Wk 0	Visit 2, 3 Wk 4, 8	Visit 4 Wk 12 EOT
ICF/HIPAA		X		
Subject Demographics/Medical Hx/Height		X		
Weight		X		X
Inclusion/Exclusion Criteria		X		
Vital Signs		X	X	X
Urine Pregnancy Test		X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>
Assessments	Acne IGA	X	X	X
	Lesion Counts <sup>2</sup>			
	Tolerability <sup>3</sup>			
Study Medication; Dispense Collect <sup>5</sup>		D	C D	C
Patient preference questionnaire				X
DLQI		X		X
Photography <sup>4</sup>		X		X
Concomitant medication/Treatment		X	X	X
Adverse Events		X	X	X

1 Female subjects of childbearing potential.

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

3 Peeling, erythema, dryness, oiliness, burning, pruritus

4. on limited subjects maximum of 5 subjects

5. count the pills and weigh the topical

#### 5.1.2 Visit 1 & 2 (Screening/Baseline Visit, Week 0)

- Informed Consent/HIPAA
- Urine Pregnancy Test (if applicable)
- Subject Demographics/Medical History
- Vital Signs with height and weight
- Concomitant Medication/Treatment
- Photography
- Adverse events
- Investigator Assessments
  - IGA, Lesion Counts, Signs and Symptoms of tolerability (peeling, erythema, dryness, oiliness)
- Inclusion/Exclusion Criteria
- Subject Assessments
  - Signs and Symptoms (burning, pruritus)

- DLQI
- Dispense study medication

### 5.1.3 Visits 2, 3, (Week 4, 8 ± 3 days)

- Urine Pregnancy Test (if applicable)
- Concomitant Medication/Treatment
- Adverse Events
- Investigator Assessments
  - Lesion Counts, IGA, Signs and Symptoms of tolerability
- Subject Assessments
  - Signs and Symptoms
- Vital signs
- Study Medications Collect and dispense

### 5.1.5 Visits 4 EOT (Weeks 12 ± 3 days)

- Concomitant Medication/Treatment
- Adverse Events
- Urine Pregnancy Test (if applicable)
- Vital Signs with weight
- Photography
- Investigator Assessments
  - Lesion Counts, IGA, Signs and Symptoms of tolerability
- Subject Assessments
  - Signs and Symptoms
  - DLQI
  - Patient Preference questionnaire
- Study Medications collect

## 5.2 Study Treatment

### 5.2.1 Details of Study Treatment

One ORACEA Capsule (40 mg) should be taken once daily in the morning on an empty stomach, preferably at least one hour prior to or two hours after meals

Active ingredient: doxycycline Inactive ingredients: hypromellose, iron oxide red, iron oxide yellow, methacrylic acid copolymer, polyethylene glycol, Polysorbate 80, sugar spheres, talc, titanium dioxide, and triethyl citrate.

Each gram of EPIDUO FORTE gel contains 3 mg (0.3%) adapalene and 25 mg (2.5%) benzoyl peroxide in a white to very pale yellow, opaque gel. EPIDUO FORTE is available in pumps containing 15 g, 30 g, 45 g, 60 g or 70 g.

EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% is a white to very pale yellow, opaque gel for topical use containing adapalene 0.3% and benzoyl peroxide 2.5%.

Adapalene, a synthetic retinoid, is a naphthoic acid derivative with retinoid-like properties. The chemical name for adapalene is (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid).

Adapalene: Molecular formula: C<sub>28</sub>H<sub>28</sub>O<sub>3</sub> Molecular weight: 412.5

Benzoyl Peroxide is a highly lipophilic oxidizing agent that localizes in both bacterial and

keratinocyte cell membranes. The chemical name for benzoyl peroxide is dibenzoyl peroxide. Benzoyl Peroxide: Molecular formula: C<sub>14</sub>H<sub>10</sub>O<sub>4</sub> Molecular weight: 242.23

EPIDUO FORTE gel contains the following inactive ingredients: acrylamide/sodium acryloyldimethyltaurate copolymer, docusate sodium, edetate disodium, glycerin, isohexadecane, poloxamer 124, polysorbate 80, propylene glycol, purified water, and sorbitan oleate.

### **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 or dosages of study medications since the previous visit and will quantify the subject's response. Also, Oracea capsules will be collected and counted as well as Epiduo Forte will be collected and weighed at each visit before dispensation.

### **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**

**Primary Efficacy Variable:** The percent of subjects who become clear or almost clear on the IGA scale

**Secondary Efficacy Variables** Secondary endpoints: 1. The percent of subjects who have at least a 2 grade or more improvement on IGA score. 2. Median percent reduction in inflammatory, non-inflammatory and total lesion count.

### **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 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
- IV Patient satisfaction

**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:

<b>Medication</b>	<b>Wash-Out Period/Restrictions</b>
<b>Topical Medications on Face</b> <ul style="list-style-type: none"> <li>▪ <i>Retinoids</i></li> <li>▪ <i>Rx Acne Medications (e.g., BPO, antibiotics)</i></li> <li>▪ <i>OTC Products that contains active ingredients (e.g., BPO washes, BPO lotions, sal acid, etc.)</i></li> <li>▪ <i>Corticosteroids</i></li> </ul>	14 days prior to Visit 1 14 days prior to Visit 1 7 days prior to Visit 1 14 days prior to Visit 1
<b>Systemic Medications</b> <ul style="list-style-type: none"> <li>▪ <i>Antibiotics (indicated for acne vulgaris , no wash out if it is used for sore throat or any other infectious process)</i></li> <li>▪ <i>Corticosteroids (indicated for acne vulgaris)</i></li> <li>▪ <i>Antimalarial medications</i></li> <li>▪ <i>Oral dapsone</i></li> <li>▪ <i>Retinoids</i></li> </ul>	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
<b>Isotretinoin</b>	6 months
<b>OTC Acne Products without any active ingredients (e.g. apricot scrubs)</b>	1 Day washout prior to Visit 1
<b>Investigational Drugs</b>	30 Day washout prior to Visit 1
<b>Cosmetic / Surgical Procedures complementary to the treatment of facial acne, such as cryotherapy or superficial peels</b>	2 Weeks

## **SUPPLEMENT II**

### **Study Treatment Application Procedure**

**EPIDUO FORTE** Apply a thin layer of EPIDUO FORTE gel to affected areas of the face and/or trunk once daily after washing. Use a pea-sized amount for each area of the face (e.g., forehead, chin, each cheek). Avoid the eyes, lips and mucous membranes.

**ORACEA:**

One ORACEA Capsule (40 mg) should be taken once daily in the morning on an empty stomach, preferably at least one hour prior to or two hours after meals

**CLEANSING AND MOISTURIZING:**

Continue routine cleansing and moisturizing as before the study.

## **Supplement III**

### **Investigator Global Assessment (IGA)**

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

**lesions counts:**

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

**SUPPLEMENT IV:**

**Patient Satisfaction for the Regimen:**

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1. How satisfied are you with this regimen in treating your acne? \_\_\_\_\_

- 1 = Very Satisfied
- 2 = Satisfied
- 3 = Somewhat Satisfied
- 4 = Dissatisfied
- 5 = Very Dissatisfied

2. Overall, how likely are you to recommend this regimen to a friend? \_\_\_\_\_

- 1 = Very Likely
- 2 = Likely
- 3 = Somewhat Likely
- 4 = Unlikely
- 5 = Very Unlikely

**PATIENT SATISFACTION FOR EPIDUO FORTE GEL:**

1. How satisfied are you with this product in treating your acne? \_\_\_\_\_
2. How satisfied are you with how easy this product is to use? \_\_\_\_\_
3. How satisfied are you with this product compared to other products you have previously used for acne, such as gels and creams? \_\_\_\_\_
4. How satisfied are you with how this product feels on your skin after treatment? \_\_\_\_\_
5. How satisfied are you with the odor of this product after treatment? \_\_\_\_\_
6. How satisfied are you with the color of this product after treatment? \_\_\_\_\_
7. Overall, how satisfied are you with this product? \_\_\_\_\_
8. Overall, how likely are you to recommend this product to a friend? \_\_\_\_\_

**Answers to Questions 1 through 7 will be selected from the following:**

- 1 = Very Satisfied
- 2 = Satisfied
- 3 = Somewhat Satisfied
- 4 = Dissatisfied
- 5 = Very Dissatisfied

**The answer to Question 8 will be selected from the following:**

- 1 = Very Likely
- 2 = Likely
- 3 = Somewhat Likely
- 4 = Unlikely
- 5 = Very Unlikely