

## **PILOT STUDY PROTOCOL**

**Protocol Title**                      **Efficacy and Safety of Aczone 7.5% gel in the Treatment of Truncal Acne Vulgaris**

**Protocol Number**                      **ACZ1601**

**Protocol Date**                      **June 1, 2016**

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## 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

Truncal acne is an under diagnosed and under treated condition. Aczone gel 7.5% has already been approved for the treatment of acne vulgaris. However, topical treatment of truncal acne is very difficult in traditional vehicles due to the difficulty of covering large body surface areas. The recent approval of Aczone gel 7.5% foam gives us an opportunity to address this unmet need. Therefore, the current pilot study will investigate the efficacy and safety of Aczone 7.5% gel in the treatment of truncal acne.

Truncal acne is estimated to occur in 61 percent and 45 percent of acne patients, respectively.<sup>1,2</sup> The pathophysiology of truncal acne is the same as facial acne, and both respond similarly to therapy.<sup>3</sup>

However, despite a wide range of treatment options available, the management of truncal acne remains challenging. Clinicians tend to emphasize oral therapies over topical interventions for truncal acne as it is typically assumed oral medications are more convenient than applying topical applications to large and potentially hard-to-reach body areas.<sup>4</sup> This line of reason is based on using standard creams or gels and does not necessarily hold-up with the advent of foam formulations that are significantly more convenient in treating hard-to-reach areas and larger surface areas. In fact, foam vehicles are associated with improved usability, better adherence and, consequently, improved therapeutic results.<sup>5,6,7,8,9,10,11,12</sup> Aczone gel 7.5% has been approved by the FDA for the treatment of acne vulgaris in individuals who are older than 12 years of age. Aczone gel 7.5% have been used on the chest and back acne during the phase III clinical trials but its efficacy has not been an endpoint in this study. It is reasonable to assume that Aczone gel 7.5% could present to be a viable treatment option for truncal acne. The current pilot study will investigate the efficacy and safety of Aczone gel 7.5% in the treatment of truncal acne. Based on the recent phase III clinical study of aczone gel 7.5%, it is expected that the typical risk/benefit profile of aczone gel 7.5% should apply in the treatment of truncal acne (ie, reduction in acne signs and symptoms, with possible adverse effects such as burning, stinging, tingling, pruritus, dry skin, erythema and/or edema).

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4. Hassan J, Grogan S, Clark-Carter D, Richards H, Yates VM. *The individual health burden of acne: appearance-related distress in male and female adolescents and adults with back, chest and facial acne. J Health Psychol.* 2009 Nov;14(8):1105-18.
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  7. DelRosso, JQ, "Management of truncal acne vulgaris: current perspectives on treatment" *Cutis*. 2006 May;77(5):285-9
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  11. Savage, LJ, Laton, AM "Treating acne vulgaris: Systemic, local and combination therapy" *Expert Rev Clin Pharmacol*. 2010;13(4):563-580
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## **1.2 Study Population**

Thirty (30) subjects with acne vulgaris with moderate truncal acne.

## **2 STUDY OBJECTIVES**

The objectives of this study are to observe the efficacy and safety of Aczone gel 7.5% as a treatment modality for moderate truncal acne.

## **3 STUDY DESIGN**

This is a three-center, open-label pilot study (Leon Kircik, MD Louisville, KY, James DelRosso, DO, Las Vegas, NV & Emil Tanghetti, MD Sacramento, CA.) . All study subjects will receive Aczone gel 7.5% at Visit 1. The duration of the study is 16 weeks and consists of a Screening, Baseline Visit, and three (3) Follow-up Visits at Weeks 4, 10, and 16.

## **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. 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. Truncal acne IGA score of 3.
- 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 medication (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

#### 5.1.1 Assessment Schedule

		Screening/ Baseline	Follow-up Visits	
		Visit 1 Wk 0	Visit 2, 3 Wk 4, 10	Visit 4 Wk 16
ICF/HIPAA		X		
Subject Demographics/Medical Hx/Height		X		
Weight		X		X
Inclusion/Exclusion Criteria		X		
Physical Exam		X		
Vital Signs		X	X	X
Urine Pregnancy Test		X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>
Assessments	Truncal Acne IGA	X	X	X
	Truncal Lesion Counts <sup>2</sup>			
	Tolerability <sup>3</sup>			
Study Medication; Dispense Collect		D	C D	C
Patient preference questionnaire				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

#### 5.1.2 Visit 1 (Screening / Baseline Visit)

- Informed Consent/HIPAA
- Urine Pregnancy Test (if applicable)
- Subject Demographics/Medical History/Height
- Weight
- Vital Signs
- Concomitant Medication/Treatment
- Assessments
  - Truncal Acne IGA
  - Truncal Lesion Counts
  - Tolerability
- Inclusion/Exclusion Criteria
- Dispense study medication and instruct regarding application procedures

### **5.1.3 Visits 2, 3, (Weeks 4, & 10 ± 3 days)**

- Concomitant Medication/Treatment
- Urine Pregnancy Test (if applicable)
- Adverse Events
- Vital Signs
- Assessments
  - *Truncal Acne IGA*
  - *Truncal Lesion Counts*
  - *Tolerability*

### **5.1.4 Visit 4 (Week 16; ± 5 days)**

- Urine Pregnancy Test (if applicable)
- Concomitant Medication/Treatment
- Adverse Events
- Vital Signs
- Weight
- Assessments
  - *Truncal Acne IGA*
  - *Truncal Lesion Counts*
  - *Tolerability*
- Collect Study Medication
- Patient preference questionnaire

## **5.2 Study Treatment**

### **5.2.1 Details of Study Treatment**

**ACZONE** (dapson) Gel, 7.5%, contains dapson, a sulfone, in an aqueous gel base for topical dermatologic use. **ACZONE** Gel, 7.5% is an off-white to yellow gel with suspended particles. Chemically, dapson has an empirical formula of  $C_{12}H_{12}N_2O_2S$ . It is a white or slightly yellow-white, crystalline powder that has a molecular weight of 248.30. Each gram of **ACZONE** Gel, 7.5%, contains 75 mg of dapson, USP, in a gel of diethylene glycol monoethyl ether, methylparaben, acrylamide/sodium acryloyldimethyl taurate copolymer, isohexadecane, polysorbate 80, and purified water.

### **5.2.2 Storage and Handling**

Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]. Protect from freezing.

### **5.2.3 Dispensation and Dosage Schedule**

**ACZONE** Gel is an off-white to yellow gel with suspended particles. It is supplied in an airless pump containing a polypropylene bottle with a high density polyethylene piston. **ACZONE** (dapson) Gel, 7.5%, is supplied in 90 gram pump (NDC 0023-5206-90). After the skin is gently washed and patted dry, apply approximately a pea-sized amount of **ACZONE** Gel, 7.5%, in a thin layer to the entire affected areas on the trunk once daily. Rub in **ACZONE** Gel, 7.5%, gently and completely.

#### **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 medication will be used. Medication 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.



## 6 STUDY ASSESSMENTS

### 6.1 Primary Endpoint

The primary endpoint of this study is the percent of patients who achieve a two grade improvement and clear or almost clear on IGA scale for truncal acne.

#### 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 reduction in inflammatory lesion count at week 16 compared to baseline.
2. Percent reduction in non-inflammatory lesion count at week 16 compared to baseline.
3. Percent reduction in total lesion count at week 16 compared to baseline.

#### 6.2.2 Tolerability

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 current severity of pruritus and burning; 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 30 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:

Medication		Washout
Topical	Retinoids, antibiotics, BPO, dapstone, bleaching agents	2Weeks washout prior to V1
	OTC acne medications or bleaching agents	1Week washout prior to V1

Oral Antibiotics for acne	<b>4Weeks</b> washout prior to V1
Oral Retinoids	<b>24Weeks</b> washout prior to V1
Cryotherapy, chemical peels, microdermabrasion	<b>2Weeks</b> washout prior to V1
Laser Resurfacing and dermabrasion	<b>24Weeks</b> washout prior to V1
Investigational Drugs	<b>4Weeks</b> washout prior to V1

## SUPPLEMENT II

### Patient's Preference Questionnaire

The aim of this questionnaire is to find out what you like and what you don't like about different types of skin medications that you have used.

- For all skin medicines you have used in the past, please rate the following treatments in the order you preferred them:

(1= "liked the best", 2= "second best", 3= "third best", 4= "fourth best, 5= "liked the least". If you have not used a certain type of skin medicine, please enter N/A for does not apply to me.)

Gel\_\_\_\_ Lotion\_\_\_\_ Cream\_\_\_\_ Ointment\_\_\_\_ Spray\_\_\_\_

- Please rate the following qualities of the gel, compared to the other skin medicines you have used in the past

(If you have not had a previous experience with other skin medicines, please circle N/A for does not apply to me.)

	Very Inferior "Much Worse"	Inferior "Worse"	About the same	Better	Superior "Much Better"	Does Not Apply to Me
Gel is easy to use	1	2	3	4	5	N/A
I am able to continue daily activities right away following putting the medicine on my skin (i.e., getting dressed, doing school work, playing etc.)	1	2	3	4	5	N/A
The gel leaves my skin feeling soft	1	2	3	4	5	N/A
I am able to apply the gel to large body surface areas	1	2	3	4	5	N/A
The gel disappears into my skin quickly when I apply it	1	2	3	4	5	N/A

- Please rate the gel on each of the following:

	Very Poor	Poor	Fair	Good	Excellent	Does Not Apply to Me
Moisturizing ("It leaves my skin feeling soft and smooth")	1	2	3	4	5	N/A
Lack of residue ("There is nothing left on my skin")	1	2	3	4	5	N/A
Does not feel greasy	1	2	3	4	5	N/A
Absorbs quickly ("Disappears into my skin quickly after I put it on my skin")	1	2	3	4	5	N/A
Easy to apply	1	2	3	4	5	N/A
Fragrance-free ("Does not smell")	1	2	3	4	5	N/A
Spread ability ("Spreads easily on my skin")	1	2	3	4	5	N/A
Lack of stickiness ("No sticky feeling")	1	2	3	4	5	N/A