Protocol Number: ACU-D1-201

A RANDOMIZED, DOUBLE-BLIND, VEHICLE CONTROLLED, PROOF-OF-CONCEPT STUDY OF THE SAFETY AND EFFICACY OF ACU-D1 OINTMENT [redacted] IN SUBJECTS WITH ACNE ROSACEA

Sponsor

Accuitis, Inc.
1005 Alderman Drive
Suite 104
Alpharetta, GA 30005
[redacted]

Study Contact

[redacted]

Medical Monitor

[redacted]

Protocol Date

28-JUN-2017

INVESTIGATOR/SPONSOR AGREEMENT

I have read this protocol and agree to conduct this clinical trial in compliance with the protocol and any applicable revisions.

Investigator Signature _____ Date _____

Investigator Printed Name _____

[redacted]

Rick Coulon
President & Chief Executive Officer
Accuitis, Inc.

8-8-2017
Date

Table of Contents

1. SYNOPSIS

Title:
A Randomized, Double-Blind, Vehicle Controlled, Proof of Concept Study of the Safety and Efficacy of ACU-D1-201 Ointment [redacted] in Subjects with Acne Rosacea.

Objectives:
The main objective of this study is to evaluate the safety, tolerability and efficacy of ACU-D1 Ointment [redacted] when applied twice daily for 12 weeks to papulopustular, Type-2, rosacea (acne rosacea) of the face.

Methodology/Study Design:
This study incorporates a randomized, double-blind, vehicle controlled, parallel-group design.

During this study, the subjects will apply ACU-D1 Ointment [redacted] or ACU-D1 Ointment Vehicle to acne rosacea of the face twice daily during a 12-week treatment period.

Approximately 36 subjects will be assigned to a study medication treatment group in a 2:1 ratio (24 to ACU-D1 Ointment [redacted]; 12 to ACU-D1 Ointment Vehicle) at multiple United States investigational centers.

The duration of study participation is anticipated to be a maximum of 116 days per subject. The final study visit (Visit 7) has a maximum allowable visit window of 4 days.

Study visits are:

- Visit 1 (Day -13 to 0) enrollment and start of the screening period
- Visit 2 (Day 1) randomization and start of the study medication treatment period
- Visit 3 (Day 15) treatment period follow-up
- Visit 4 (Day 29) treatment period follow-up
- Visit 5 (Day 57) treatment period follow-up
- Visit 6 (Day 85) end of the treatment period and start of the no treatment follow-up period
- Visit 7 (Day 99) no treatment follow-up, end of study.

During Visit 1, the investigator determines eligibility of potential subjects for study enrollment and will, for eligible subjects, conduct the procedures to determine her/his eligibility for randomization.

At Visit 2, eligible subjects will be randomized to a study medication treatment group, will initiate twice daily applications for the 12-week treatment period and will perform the first study medication while being observed by an investigational center staff member.

At Visits 3-5, subjects will be seen for treatment period follow-up.

At Visit 6, subjects will be seen for end of the treatment period follow-up and will start the 2-week no treatment follow-up period.

At Visit 7, subjects will be seen for a no treatment follow-up and be discharged from the study.

Number of Subjects:
Approximately 36 subjects will be enrolled in this study at multiple United States investigational centers. Subjects will be randomized in a 2:1 ratio with the goal to have 24 subjects randomized to treatment with ACU-D1 Ointment [redacted] and 12 subjects randomized to treatment with ACU-D1 Ointment Vehicle.

Diagnosis and Main Criteria for Inclusion:
Subjects will be adult males and females with a clinical diagnosis of papulopustular rosacea of the face that includes a total of ≥10 and ≤40 papules, pustules and nodules with ≤2 nodules.

Study Medications, Application, and Mode of Administration:
There are 2 study medications:

- ACU-D1 Ointment [redacted]
- ACU-D1 Ointment Vehicle.

There are 2 treatment groups:

- ACU-D1 Ointment [redacted] applied twice daily for 12 weeks
- ACU-D1 Ointment Vehicle applied twice daily for 12 weeks.

Subjects will be assigned to one of the two treatment groups, in a blinded manner, in a 2:1 ratio, 24 subjects will be assigned to receive ACU-D1 Ointment [redacted] and 12 subjects will be assigned to receive ACU-D1 Ointment Vehicle.

Subjects will apply the assigned study medication twice daily during a 12-week treatment period.

Duration of Study:
The planned treatment and study durations are:

- Enrollment period: approximately 84 days (12 weeks)
- Subject participation period: up to 116 days
- Study duration (first subject first visit, through last subject last visit): approximately 200 days.

Evaluations – Efficacy:
The investigator will perform a Lesion Count of papules, pustules and nodules and an Investigator's Global Assessment (IGA), a static assessment of the average overall severity of papulopustular rosacea on the face, to evaluate the status of the rosacea throughout the study.

Evaluations – Safety:
Adverse events, local tolerability of signs and symptoms of irritation, clinical laboratory safety tests, vital sign readings and urine pregnancy tests will be monitored throughout the study.

Evaluations – Other:
Standardized color photographs of the subject's face to document the status of the rosacea being treated will be taken throughout the study.

Statistical Methods:
The goal of the statistical analysis is to assess evidence of an overall effect of twice-daily ACU-D1 in the therapy of subjects with papulopustular rosacea. Next a set of planned pair-wise comparisons will be made evaluating the active dose against vehicle. Two types of study populations will be analyzed, namely, the Intention-To-Treat (ITT) and the Per-Protocol populations. The definitions of the populations for the different types of analyses follow those given in the ICH E9 guideline (1998).

Safety analyses will include descriptive statistics calculated on the safety parameters using the ITT population. The proportion of subjects with treatment-emergent adverse events will be tabulated and presented by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class. Vital signs, Local Tolerability Assessment (LTA) scores and clinically relevant abnormal laboratory results will also be tabulated and presented. Where applicable data will be listed and summarized by visit.

Safety summaries will include listings of adverse event incidences within each MedDRA System Organ Class, and changes from pre-application values in vital signs. Adverse event summaries will be presented showing the proportion of subjects experiencing adverse events, both overall and by MedDRA System Organ Class.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
°C	Degrees Celsius
CFR	Code of Federal Regulations
CR	Clinically Relevant
CRA	Clinical Research Associate
CRO	Contract Research Organization
e.g.	for example (*Latin; exempla gratia*)
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
i.e.	that is
Inc.	Incorporated
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LTA	Local Tolerability Assessment
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified intent-to-treat
mL	Milliliter

Abbreviation	Term
NCR	Not Clinically Relevant
OTC	Over-the-counter
SAE	Serious Adverse Event
SAS	Statistical Analyses System
SI	Subject Identifier
SOP	Standard Operation Procedure
US	United States
WOCBP	Woman of childbearing potential

2. INTRODUCTION

2.1. Introduction and Background

Rosacea is one of the most commonly occurring dermatoses treated by dermatologists today. Rosacea is an inflammatory condition of the skin, classically presenting with flushing and/or blushing along with erythema, edema, telangiectasia, papules, pustules and nodules of the face.[1]

ACU-D1 [pentaerythritol tetrakis (3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate) (PTTC)] may be beneficial in the treatment of inflammatory lesions in patients with rosacea based on its anti-inflammatory properties.

2.2. Study Rationale

This study is designed to evaluate the safety and efficacy of ACU-D1 Ointment (PTTC) [redacted] and a matching ointment vehicle in the treatment of the inflammatory lesions of the face associated with Type-2 (papulopustular) rosacea.

3. STUDY OBJECTIVES

The main objective of this study is to evaluate the safety, tolerability and efficacy of ACU-D1 Ointment [redacted] when applied twice daily for 12 weeks to papulopustular (Type-2) rosacea (acne rosacea) of the face.

4. SELECTION AND DISPOSITION OF STUDY POPULATION

4.1. Number of Subjects

Approximately 36 subjects will be enrolled in this study at multiple United States investigational centers. Subjects will be randomized in a 2:1 ratio with 24 subjects randomized to treatment with ACU-D1 Ointment [redacted] and 12 subjects randomized to treatment with ACU-D1 Ointment Vehicle. Subject enrollment will be competitive.

4.2. Study Population Characteristics

Male and female subjects, 18 years of age or older who meet all the inclusion criteria and none of the exclusion criteria will be allowed to enroll in this study.

4.3. Inclusion Criteria

To be eligible for enrollment at Visit 1 the subject must fulfill all the following inclusion criteria:

1. Subject is at least 18 years of age
2. Subject has a clinical diagnosis of stable papulopustular rosacea (type-2)
3. Subject has a total of ≥10 and ≤40 inflammatory lesions (papules, pustules and nodules) on the face
4. Subject has a ≤2 nodules on the face
5. Subject has an Investigator's Global Assessment score of ≥3
6. If the subject is a woman of childbearing potential, she has a negative urine pregnancy test and agrees to use an approved effective method of birth control for the duration of the study
7. Subject is non-pregnant and non-lactating
8. Subject is in good general health and free of any known disease state or physical condition which, in the investigator's opinion, might impair evaluation of rosacea or which exposes the subject to an unacceptable risk by study participation
9. Subject is willing and able to follow all study instructions and to attend all study visits
10. Subject is able to comprehend and willing to sign an Informed Consent Form.

4.4. Exclusion Criteria

Any potential subject who meets one or more of the following criteria will not be included in this study:

1. Subject is pregnant, nursing or planning to become pregnant during the duration of the study
2. Subject has used systemic glucocorticosteroids within 42 days prior to Visit 1 (inhaled and ocular glucocorticosteroids are permitted)
3. Subject has used systemic antibiotics within 28 days prior to Visit 1
4. Subject has used any topical glucocorticosteroids on the face within 28 days prior to Visit 1
5. Subject has used any prescription or over-the-counter (OTC) product for the treatment of acne or rosacea within 14 days prior to Visit 1
6. Subject is currently using any therapy that, in the investigator's opinion, is a photosensitizer (*e.g.*, phenothiazines, amiodarone, quinine, thiazides, sulphonamides, quinolones, etc.)
7. Subject currently has any skin disease (*e.g.*, psoriasis, atopic dermatitis, eczema), or condition (*e.g.*, actinic keratosis, photo-damage, sunburn, excessive hair, open wounds) that, in the investigator's opinion, might impair evaluation of rosacea or which exposes the subject to an unacceptable risk by study participation

8. Subject currently has, on the face, or has had on the face, any of the following within the specified period prior to Visit 1 that, in the investigator's opinion, might impair evaluation of rosacea or which exposes the subject to an unacceptable risk by study participation:
    - A cutaneous malignancy; 180 days
    - Experienced a sunburn; 14 days
9. Subject has facial hair, that in the investigator's opinion, might impair evaluation of rosacea or proper study medication application
10. Subject has a history of sensitivity to any of the ingredients in the study medications
11. Subject has participated in an investigational drug trial in which administration of an investigational study medication occurred within 30 days prior to Visit 1.

4.5. Previous and Concomitant Therapies

4.5.1. Previous therapies

During Visit 1, subjects will be questioned to ensure they have not used any excluded therapies.

4.5.2. Concomitant therapies

Concomitant therapies are any new or existing therapy received by the subject after signing the ICF until discharge from the study.

Concomitant therapies include drug (*e.g.*, prescription and OTC) and non-drug (*e.g.*, chiropractic, physical therapy, energy-based treatments) therapies. Subjects will refrain from receipt of any therapy in accord with the inclusion/exclusion criteria. Subjects will also refrain from changing the use of any concomitant therapies during the duration of the study.

All new or modified concomitant therapy used during the study must be recorded.

Any new or modified concomitant therapy must be considered to determine if it is related to an AE. An AE must be reported unless the therapy is added or modified for non-medical reasons (*e.g.*, health insurance purposes) or it is for prophylaxis (*e.g.*, vaccinations).

A frequency of "as needed" (PRN) is not acceptable when reporting concomitant therapies.

4.5.3. Prohibited therapies

During this study, subjects are prohibited from using therapies listed in the exclusion criteria.

Starting with Visit 2 subjects are prohibited from applying any leave-on topical products, including but not limited to, lotions, creams, ointments, the investigator approved bland, non-medicated emollient/moisturizer and cosmetics to the treatment area within 8 hours prior to a study visit. The subject's routine cleansers are allowed.

The investigator should notify the Accuitis, Inc. Medical Monitor within 24 hours if any prohibited therapy is required to ensure subject safety.

4.6. Subject Discontinuation from the Study

Subjects will be informed that they are free to withdraw from the study at any time and for any reason.

The investigator may remove a subject from the study if, in the investigator's opinion, it is not in the best interest of the subject to continue the study. Subjects may be discontinued due to occurrence of AEs, occurrence of pregnancy or use of a prohibited concomitant therapy. The investigator will notify the Accuitis, Inc. study monitor within 24 hours of any subject discontinuation.

In case of premature discontinuation of study participation, efforts will be made to perform all the Visit 6 assessments for discontinuations during the treatment period and all the Visit 7 assessments for discontinuations during the no-treatment period. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's case report forms (CRFs). All withdrawn subjects with ongoing AEs will be followed as appropriate.

The study may be discontinued at the discretion of the investigator or Accuitis, Inc. Some examples of reasons for discontinuation are the occurrence of the following:

- Increased frequency, severity or duration of known AEs
- Medical, regulatory or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of subjects
- Cancellation of the drug development program.

4.7. Subject Identifier (SI)

The investigator will assign a unique four-digit Subject Identifier (SI) to each subject at Visit 1.

The SI format will be NN-NN where the first two digits are the investigational center site number and the final two digits are the Subject Number (SN). The investigator center number will be provided by Accuitis and the SN must be assigned in ascending numerical order, without omitting or repeating any number, starting with 01 at each investigational center. For example, the SI for the second subject assigned at site number 2 would be 02-02.

The subject will be identified using the SI in all study documentation for the duration of the study.

4.8. Replacement Subjects

Subject enrollment will continue until approximately 36 subjects have been randomized. Subjects who are randomized and do not complete the study will not be replaced.

5. INVESTIGATIONAL PLAN

5.1. Study Design

This is a randomized, double-blind, vehicle-controlled, parallel-group study of ACU-D1 Ointment [redacted] and the ACU-D1 Ointment Vehicle in subjects with papulopustular rosacea on the face.

The study will be conducted at multiple United States investigational centers.

Study visits are:

- Visit 1 (Day -13 to 0) enrollment and start of the screening period
- Visit 2 (Day 1) randomization and start of the study medication treatment period
- Visit 3 (Day 15) treatment period follow-up
- Visit 4 (Day 29) treatment period follow-up
- Visit 5 (Day 57) treatment period follow-up
- Visit 6 (Day 85) end of the treatment period and start of the no treatment follow-up period
- Visit 7 (Day 99) no treatment follow-up, end of study.

During Visit 1, the investigator determines eligibility of potential subjects for study enrollment and will, for eligible subjects, conduct the procedures to determine her/his eligibility for randomization.

At Visit 2 eligible subjects will be randomized to a study medication treatment group in a 2:1 ratio (ACU-D1 Ointment [redacted]: ACU-D1 Ointment Vehicle). Subject's will initiate twice daily applications for the 12-week treatment period and will perform the first study medication while being observed by an investigational center staff member.

At Visits 3-5 subjects will be seen for treatment period follow-up.

At Visit 6, subjects will be seen for end of the treatment period follow-up and will start the 2-week no treatment follow-up period.

At Visit 7, subjects will be seen for a no treatment follow-up and be discharged from the study.

5.2. Subject Instructions

At Visit 1 a study staff member will dispense a Subject Instruction sheet to each subject.

During the entire duration of the study subjects must:

- Continue to use her/his routine facial cleansers and cosmetics except she/he many only use an investigator approved bland, non-medicated emollient/moisturizer (*e.g.*, Cetaphil®)
- Not apply any leave-on topical products including, but not limited to lotions, creams, ointments, investigator approved bland, non-medicated emollient/moisturizer and cosmetics, to the treatment area within 8 hours prior to a study visit (the subject's routine cleansers are allowed)
- Avoid exposing her/his face to excessive natural (*e.g.*, sunlight) or artificial (*e.g.*, tanning beds) ultraviolet radiation and use her/his routine sunscreen if excessive exposure cannot be avoided
- Continue her/his routine cleansers and cosmetics
- Bring the subject instruction sheet to every visit.

During the 12-week treatment period, subjects must:

- Apply the study medication to her/his entire face from the hairline down to the jaw line and from ear to ear as directed, twice daily, with at least 8 hours between each application
- Not apply the study medication to the eyes, eyelids, any membrane of the inner nose, mouth, lips and open wounds
- Not apply the study medication within 6 hours prior to any study visit
- Not wash or submerge the treated area for at least 4 hours after a study medication application
- Not apply any topical products to the treatment area for at least 20 minutes after a study medication application

- Not allow anyone else to use your study medication
- Keep the study medication away from children
- Keep the study medication refrigerated when it is not being used for an application and use the cooler provided by the investigational staff (or equivalent) to transport the study medication
- Bring her/his study medication to every study visit.

5.3. Study Flow Chart

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Protocol**
Day	**-13 to 0**	**1**	**15**	**29**	**57**	**85**	**99**	**Section**
Informed consent	X							11.3
Subject identifier	X							4.7
Inclusion/exclusion criteria	X							4.3/4.4
Demographics	X							6.3.1
Medical history	X							6.3.2
Vital signs	X	X					X	6.2.3
Urine pregnancy tests	X						X	6.2.4
Lesion count	X	X	X	X	X	X	X	6.1.1
Investigator's global assessment	X	X	X	X	X	X	X	6.1.2
Local tolerability assessment		X[1]	X	X	X	X	X	6.2.2
Clinical laboratory samples	X					X		6.2.1
Identify investigator approved emollient/moisturizer	X							4.5.2
Standardized photography		X	X	X	X	X	X	6.3.3
Randomization		X						5.6.4
Dispense/collect study medication		X	X	X	X	X		5.6.5
Study medication treatment		⟷						5.6.6
No treatment Follow-up							⟷	5.6.6
Subject instructions	X	X	X	X	X	X		5.2
Concomitant therapies	X	X	X	X	X	X	X	4.5.2
Adverse events		X	X	X	X	X	X	7

[1]Local tolerability assessments will be performed before and after the first study medication application

5.4. Study Visits Description and Procedures

A written, signed informed consent form (ICF) must be obtained from every subject prior to performing any study related procedure (*i.e.*, vital signs, clinical laboratory sampling, urine pregnancy test or photography).

5.4.1. Visit 1 (Day -13 to 0); enrollment

The following procedures will be performed at Visit 1.

At this visit, the investigator or designee will:

1. Review and explain the nature of the study to the subject, particularly the prohibited activities and the time/logistical constraints, obtain the subject's signature on the appropriate approved ICF and Health Insurance Portability and Accountability Act (HIPAA) authorization and provide a copy to the subject
2. Assign a SI to each subject
3. Confirm the subject meets all the inclusion criteria and none of the exclusion criteria
4. Collect demographic information
5. Collect medical history information
6. Measure vital signs
7. Perform a urine pregnancy test for women of childbearing potential (WOCBP); a negative result is required
8. Report concomitant therapies information
9. Perform a Lesion Count; a total of ≥10 and ≤40 inflammatory lesions (papules, pustules and nodules) with ≤2 nodules on the treatment area is required
10. Perform an IGA; a score of ≥3 (moderate to severe) is required
11. Collect blood samples for clinical laboratory evaluations
12. Identify an investigator approved bland, non-medicated emollient/moisturizer
13. Review the study instructions with the subject and dispense a Subject Instruction sheet
14. Schedule Visit 2.

5.4.2. Visit 2 (Day 1); randomization and start of treatment period

This visit should occur within 14 days after Visit 1. Subsequent study visit dates must be scheduled based on the date of this visit.

Prior to this visit the investigator/designee must confirm that all items necessary to determine the subject's eligibility for randomization are available.

At this visit, the investigator or designee will perform the following procedures PRIOR TO RANDOMIZATION:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report any changes that are, in the investigator's opinion, meaningful, as Medical History
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions
4. Measure vital signs
5. Perform a Lesion Count; a total of ≥10 and ≤40 inflammatory lesions (papules, pustules and nodules) and ≤2 nodules on the treatment area is required
6. Perform an IGA; a score of ≥3 (moderate to severe) is required
7. Determine the subject's eligibility for randomization
8. Discharge from the study subjects who are not eligible for randomization.

For subjects who are eligible for randomization the investigator or designee will perform the following procedures:

1. Take standardized color photographs
2. Have the subject perform a pre-treatment Local Tolerability Assessment (LTA)
3. Perform a pre-treatment LTA
4. Randomize eligible subjects
5. Dispense study medication to the subject
6. Instruct the subject on the proper study medication application technique
7. Observe the subject's first study medication application
8. Monitor the subject for at least 20 minutes after the Application Completion Time to detect any adverse events
9. Have the subject perform a post-treatment LTA 10 (±4) minutes after the Application Completion Time
10. Perform a post-treatment LTA 20 (±4) minutes after the Application Completion Time
11. Review the study instructions with the subject
12. Schedule Visit 3.

5.4.3. Visit 3 (Day 15); treatment period follow-up

This visit should occur 14 [±4] days after Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions
4. Perform a Lesion Count
5. Perform an IGA
6. Have the subject perform an LTA
7. Perform an LTA
8. Take standardized color photographs
9. Dispense and collect study medication as appropriate
10. Review the study instructions with the subject
11. Schedule Visit 4.

5.4.4. Visit 4 (Day 29); treatment period follow-up

This visit should occur 28 [±4] days after Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions
4. Perform a Lesion Count
5. Perform an IGA
6. Have the subject perform an LTA
7. Perform an LTA
8. Take standardized color photographs
9. Dispense and collect study medication as appropriate
10. Review the study instructions with the subject
11. Schedule Visit 5.

5.4.5. Visit 5 (Day 57); treatment period follow-up

This visit should occur 56 [±4] days after Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions
4. Perform a Lesion Count
5. Perform an IGA
6. Have the subject perform an LTA
7. Perform an LTA
8. Take standardized color photographs
9. Dispense and collect study medication as appropriate
10. Review the study instructions with the subject
11. Schedule Visit 6.

5.4.6. Visit 6 (Day 85); end of treatment period and start of no-treatment period

This visit should occur 84 [±4] days after Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions
4. Perform a Lesion Count
5. Perform an IGA
6. Have the subject perform an LTA
7. Perform an LTA
8. Collect blood samples for clinical laboratory evaluations
9. Take standardized color photographs
10. Collect all study medication
11. Review the study instructions with the subject
12. Schedule Visit 7.

5.4.7. Visit 7 (Day 99); end of study

This visit should occur 98 [±4] days after Visit 2.

The investigator must review the Visit 6 clinical laboratory test results prior to this visit.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions
4. Measure vital signs
5. Perform a urine pregnancy test for WOCBP
6. Perform a Lesion Count
7. Perform an IGA
8. Have the subject perform an LTA
9. Perform an LTA
10. Take standardized color photographs
11. Discharge the subject from the study.

5.5. Study Duration

The duration of study participation for each subject is anticipated to be a maximum of 116 days.

The maximum total study duration (including allowable visit windows) is anticipated to be approximately 200 days from the first subject's first visit to the last subject's last visit.

The study end date is the date of the last subject's last visit.

5.6. Study Medications

5.6.1. Study medication identity

The study medications are white to off-white colored ointments and are indistinguishable in physical appearance. The study medications must be maintained at the investigational center in a secure area with limited access under appropriately controlled and monitored storage conditions. Study medications must be stored in a refrigerator at the investigational center.

Study Medication Information		
Study medication name	ACU-D1 Ointment [redacted]	ACU-D1 Ointment Vehicle
Manufacturer	[redacted]	
Active ingredient	PTTC	None
Active concentration	[redacted]	0%
Pharmaceutical Form	Ointment	
Storage Conditions	[redacted]	
Dose regimen		
Route	Topical	
Frequency	Twice daily	
Duration of administration	84 days (12 weeks)	

5.6.2. Study medication packaging and labeling

The study medications will be packaged in identical appearing white plastic jars that each contain 2 ounces of study medication.

One Subject Kit that contains 3 jars of study medication will be prepared for each subject.

Subject Kits will be labeled with a two-part, three-panel, label. One part of the label remains attached to the Subject Kit, the other part (two-panel tear-off) is separated when the study medication is first dispensed to a subject.

The affixed part and the first panel of the tear-off part show at least the following:

- Subject Kit number (randomization number)
- Protocol number
- Storage conditions
- Sponsor information
- Space to enter SI
- Space to enter the subject's initials
- Space to enter the date randomized.

The second panel of the tear-off part is a blinded label (*e.g.*, sealed, tamper-evident envelope, scratch-off or equivalent) which when opened identifies the contents of the jars. The blinded label should only be opened in a medical emergency.

Each study medication jar will be labeled with a one-part label that remains attached to the jar and shows at least the following:

- Subject Kit number (randomization number)
- Protocol number
- Jar number
- Directions for use
- Investigational drug warning
- Space to enter SI
- Space to enter the subject's initials
- Space to enter date dispensed.

5.6.3. Method of treatment assignment

Prior to the start of the study, Accuitis Inc. or a designated third party will generate a list of randomization numbers that shall be transmitted to the assigned clinical packaging organization for study medication labeling. The randomization number is also the Subject Kit number.

The randomization list will be stored with access limited to designated personnel for study medication labeling. The randomization list will be made available as appropriate to unblind the database.

At Visit 2, eligible subjects will be assigned in a random manner to one of the 2 study medications in a 2:1 ratio (ACU-D1 Ointment [redacted]: ACU-D1 Ointment Vehicle).

5.6.4. Subject randomization

This is a double-blind study. At Visit 2, the investigator or designee will assign study medication to eligible subjects by selecting Subject Kits in chronological sequence and in ascending numerical order starting with the lowest available Subject Kit number (the Subject Kit number is the randomization number). The investigator will not omit or reuse any Subject Kit numbers.

The investigational center staff member randomizing the subject will enter the SI, subject initials and date randomized on both parts of the Subject Kit label, remove the tear-off part, attach it to the subject's label page CRF, and record the Subject Kit number assigned in the subject's CRF.

5.6.5. Dispensing and collecting study medication

The study medication must be dispensed only to study subjects, only at investigational centers specified on the Form FDA 1572 (or its equivalent) and only by authorized personnel as required by applicable regulations and guidelines.

At Visit 2, after the subject is randomized, locate study medication jar #1, enter the SI, subject initials and date dispensed on the jar label, and dispense the jar of study medication to the subject. Also dispense a cooler, provided by Accuitis, to each subject.

The subject must bring dispensed study medication jars with them to all visits using use the cooler provided by the investigational staff (or equivalent) to transport the study medication.

At Visits 3-5, examine the jar(s) of study medication dispensed to the subject, collect any jar that contains no useable study medication and dispense a new jar, if required, following the instructions above.

At Visit 6, collect all study medication jars from the subject.

The investigational center staff should make every effort to obtain all dispensed and unused study medication. Two documented telephone contacts followed by a registered letter to the subject are adequate follow-up efforts. If these efforts fail, the reason for the failure must be noted on the appropriate line of the study medication inventory CRF.

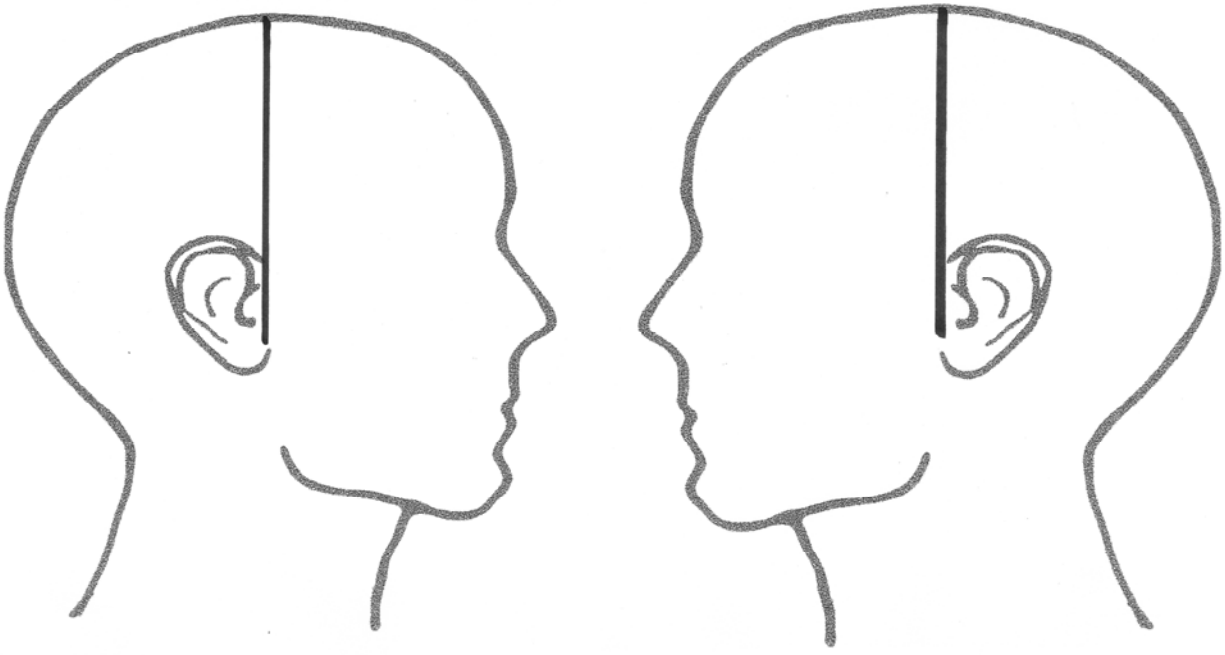
All unused and un-dispensed study medication should be held for inspection by Accuitis, Inc.'s monitor. Upon completion of the study all study medication will be returned to Accuitis, Inc. or a designated third party by the monitor using a traceable method.

5.6.6. Study medication application

The study medications are for external, topical use on the face only and on the appropriate study subject only.

The treatment area is the subject's entire face. For this study, the face is defined:

- Vertically from the mandibular ridge to the hairline (for subjects with a receding hairline the maximum "hairline" is defined by the vertical line drawn over the top of the head from tragus to tragus; see below)



Right Profile Left Profile

- Horizontally from tragus to tragus, excluding the eyes, eyelids, any membrane of the inner nose, mouth, lips and open wounds.

At Visit 2, an investigational center staff member will instruct the subject on the proposer study medication application technique, will observe the subject's first application a will monitor the subject for adverse events for at least 20 minutes after the application is completed.

To perform a study medication application the subject should:

- Wash her/his hands before starting the application
- Avoid applying the study medication to the eyes and eyelids, any membrane of the inner nose, mouth, lips and open wounds
- Apply an amount of the assigned study medication sufficient to cover the entire face with a thin layer of the medication
- Gently rub in the study medication until no visible accumulation is evident
- Wash her/his hands after completing the application.

At Visit 2, a staff member must observe the subject's study medication application to ensure proper application technique. A staff member must record the time the subject completes the application as the Application Completion Time. A staff member must monitor the subject for adverse events for at least 20 minutes after the Application Completion Time.

The subjects are to continue twice-daily application of the assigned study medication to the face for 12 weeks with at least 8 hours between applications.

After completing a study medication application subjects should not:

- Wash the treated areas for at least 4 hours
- Apply any topical products (*e.g.*, cosmetics, investigator approved bland, non-medicated emollient/moisturizer, sunscreens) to the treated area for at least 20 minutes.

Subjects should not apply the study medication within 6 hours prior to any study visit.

5.6.7. Dose compliance record

At Visits 3-6, an investigational center staff member must query each subject to determine compliance with the study medication application procedure and frequency. The staff member will document the study medication usage in the CRF.

5.6.8. Dose modification

Subjects should not modify the study medication application procedure or frequency. All application modifications must be reported on the appropriate CRF page.

If any significant study medication intolerance or safety issue occurs, after consulting with the Accuitis, Inc. Medical Monitor (see Page 1), the investigator or designee may direct the subject to reduce the study medication application frequency. If the subject cannot perform twice daily applications to the entire treatment area for more than 4 consecutive days, the subject must be removed from the study.

5.7. Study Medication Management

5.7.1. Accountability

The investigator or designee will maintain an accurate record of the receipt of the study medications as shipped by Accuitis, Inc. (or designee), including the date received and the condition of the study medications. One copy of this receipt will be returned to Accuitis, Inc. when the contents of the study medication shipment have been verified and one copy maintained in the study file. In addition, an accurate study medication disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This inventory record will be available for inspection at any time. At the completion of the study, the original inventory record will be available for review by Accuitis, Inc. upon request.

5.7.2. Return and disposition of study supplies

At the completion of the study, all unused study medication will be returned to Accuitis, Inc. (or designee) for disposal per Accuitis, Inc.'s (or designee's) written instructions.

5.8. Blinding

5.8.1. Verification of blinding

Blinding of the study medications is important for validity of this study. This study uses a double-blind design. The study medications are indistinguishable in appearance, packaging and labeling.

5.8.2. Unblinding during the study

Blinding is important for validity of this study. However, the blind may be broken in the event of a medical emergency in which knowledge of the study medication identity is critical to the management of the subject's course of treatment. Before breaking the blind the investigator should determine that the information is necessary (*i.e.*, that it will alter the subject's immediate course of treatment). In many cases, particularly when the emergency is clearly not study medication-related, the problem may be effectively managed by assuming that the subject is receiving active study medication without the need for unblinding.

If deemed necessary to break the blind for a study subject, attempt to contact the Accuitis, Inc. Medical Monitor (see Page 1) to obtain concurrence. If it is not possible to contact the Medical Monitor beforehand, contact her/him as soon as possible after breaking the blind for a subject.

To identify a subject's study medication, locate the second panel of the Subject Kit tear-off label attached to the subject's CRF and follow the unblinding instructions on the label. Record the date of unblinding, the reason for unblinding and the initials of the investigational center staff member who performed the unblinding in the subject's CRF.

Any subject whose blind has been broken must be discharged from the study.

6. STUDY ASSESSMENTS

The study assessments will be performed according to the schedules noted below by the investigator or appropriately trained study staff member as noted for each assessment. The same staff member should perform the assessments for a given subject throughout the study. If this becomes impossible, an appropriate designee with overlapping experience with the subject and study should perform the assessments.

6.1. Efficacy Evaluations

6.1.1. Lesion count

The Lesion Count is the total number of rosacea acne lesions (*i.e.*, papules, pustules and nodules) on the subject's face.

At Visits 1-7, the investigator will report the total number for each of the following lesion types on the face:

- Papules, defined as raised inflammatory lesions, <0.5cm in diameter with no visible purulent material
- Pustules, defined as raised inflammatory lesions, <0.5cm in diameter with visible purulent material
- Nodules, defined as any circumscribed, inflammatory mass ≥0.5cm in diameter.

The investigator should count each lesion type separately papules first, then pustules then nodules. She/he should start counting at the middle of a subject's forehead moving clockwise ending where she/he started, then count the number of lesions on the nose and report the total number of lesions.

At Visit 1, to be enrolled and at Visit 2 to be randomized the subject must have a total of ≥10 and ≤40 inflammatory lesions (papules, pustules and nodules) with ≤2 nodules, on the face.

6.1.2. Investigator's global assessment (IGA)

The IGA is the investigator's assessment of the average overall severity of rosacea on the subject's face at a particular point in time. The investigator should NOT refer to any other assessments to assist with these assessments.

At Visits 1-7 the investigator will the assess the rosacea on each subject's face and report the one integer that best describes the average overall severity using the scale below:

Investigator's Global Assessment	
Grade	Descriptor
0	Clear: No papules or pustules, no nodules, none or barely perceptible erythema
1	Near Clear: Very few (≤3) papules and/or pustules, no nodules, very mild erythema
2	Mild: Few papules and pustules present, no nodules, mild erythema
3	Moderate: Several papules and pustules are the predominant feature, ≤2 nodules may be present, moderate erythema
4	Severe: Numerous papules and pustules, multiple nodules may be present, severe erythema

At Visit 1, to be enrolled and at Visit 2, to be randomized, the subject must have an IGA grade of ≥3 (Moderate).

At Visit 2 the IGA must be completed prior to the start of the first study medication application.

6.2. Safety Evaluations

In addition to routine AE monitoring the following safety assessments will be performed.

6.2.1. Clinical laboratory sampling

At Visits 1 and 6 non-fasting blood samples for clinical laboratory analysis will be collected by a qualified staff member. At a minimum the following tests will be conducted:

Chemistry Panel	**Complete Blood Count**
Albumin	Hematocrit
Alkaline phosphatase	Hemoglobin
Alanine aminotransferase (ALT)	Platelet count
Aspartate aminotransferase (AST)	Red blood cell morphology
Blood urea nitrogen (BUN)	Red blood cell count
Bicarbonate	White blood cell count
Calcium	White blood cell differential
Chloride	% & absolute
Creatinine	Basophils
Glucose	Eosinophils
Lactate dehydrogenase (LDH)	Lymphocytes
Phosphorus	Monocytes
Potassium	Neutrophils
Sodium	
Total bilirubin	**Complete Urinalysis**
Total protein	
Uric acid	

The investigator or physician subinvestigator must review the results of each subject's Visit 1 clinical laboratory test results prior to Visit 2. The subject must be withdrawn from the study if any of the Visit 1 results are outside normal range for the laboratory AND, in the opinion of the reviewer, clinically relevant (CR).

The results of the clinical laboratory tests will be reported on the laboratory's standard reports. The investigator/subinvestigator must review all laboratory reports in a timely manner, noting NCR (not clinically relevant) or CR, or the equivalent, for any result that is outside the normal range for the laboratory then date and sign/initial the report.

The investigator/subinvestigator must report all laboratory results that are BOTH outside the normal range for the laboratory AND, in the opinion of the investigator/subinvestigator CR as medical history if found in the results for samples collected prior to the start of the first study medication application and as adverse events if found in the results for samples collected after the start of the first study medication application.

6.2.2. Local tolerability assessment (LTA)

The LTA is the investigator's assessment of the average overall severity of signs and the subject's assessment of the average overall severity of symptoms associated with irritation on the treated area. The investigator and subject must NOT refer to any other evaluation to assist with these assessments. This is not a comparison with the assessment at any other time point.

LTA Signs (assessed by the investigator):

- Erythema
- Scaling/dryness.

LTA symptoms (assessed by the subject):

- Stinging
- Burning
- Pruritus (itch).

At Visits 2-7, the investigator and the subject will evaluate the LTA signs and the LTA symptoms respectively.

The investigator will assess the LTA signs as follows:

- At Visit 2:
  - Prior to the first study medication application
  - 20 (±4) minutes after the Application Completion Time.
- At Visits 3-7.

The subject will assess the LTA symptoms as follows:

- At Visit 2:
  - Prior to the first study medication application report the LTA for each symptom over the previous 24 hours
  - 10 (±4) minutes after the Application Completion Time, report the LTA for each symptom since the Application Completion Time.
- At Visits 3-7:
  - Report the LTA for each symptom over the previous 24 hours.

The investigator, for the signs, should report the one integer that best describes the average overall severity on the face using the scales below:

Local Tolerability Assessment – Erythema	
Grade	Descriptor
0	Clear: No erythema present
1	Mild: Slight erythema
2	Moderate: Definite erythema
3	Severe: Marked, fiery erythema

Local Tolerability Assessment – Dryness/Scaling	
Grade	Descriptor
0	Clear: No signs of dryness or scaling
1	Mild: Slight roughness (may be more easily felt than seen), barely perceptible scaling
2	Moderate: Moderate roughness, definite scaling
3	Severe: Marked roughness, heavy scaling

The subject, for the symptoms, should report the one integer that best describes the average overall severity on the face using the scales below:

Local Tolerability Assessment – Stinging	
Grade	Descriptor
0	Clear: No stinging
1	Mild: Slight tingling, not bothersome
2	Moderate: Definite tingling, slightly bothersome
3	Severe: Intense stinging, bothersome and/or uncomfortable

Local Tolerability Assessment – Burning	
Grade	Descriptor
0	Clear: No burning
1	Mild: Slight warmth, not bothersome
2	Moderate: Definite warmth, slightly bothersome
3	Severe: Intense feeling of heat, bothersome and/or uncomfortable

Local Tolerability Assessment – Pruritus (Itching)	
Grade	Descriptor
0	Clear: No itching
1	Mild: Slight itching that is noticeable but is not bothersome
2	Moderate: Definite itching that is bothersome but does not disrupt activities or sleep
3	Severe: Intense itching this is bothersome and may disrupt activities or sleep

Follow these steps to complete the LTA for each symptom by a subject:

- An investigational center staff member, other than the evaluating investigator, will show the appropriate LTA symptom grading scale to the subject and instruct the subject on the time interval to be considered
- The staff member should not give any opinion on the meaning of the LTA descriptors
- The subject should verbally indicate the appropriate grade and the staff member will report the grade in the source document
- Both the subject and the staff member must initial and date the source document to indicate the subject performed the LTA for symptoms as instructed
- The staff member must not influence the subject's assessment.

6.2.3. Vital signs

At Visits 1, 2 and 7, a qualified investigational center staff member will measure the following vital signs:

- Body temperature
- Pulse rate
- Respiration rate
- Blood pressure (systolic and diastolic) after the subject sits quietly for at least 5 minutes
- Height (at Visit 1 only)
- Weight (at Visit 1 only).

A systolic blood pressure >140mm Hg or a diastolic blood pressure >90mm Hg is considered abnormal and therefore the investigator must define the reading as CR or NCR.

A weight of >300 pounds is considered abnormal and therefore the investigator must define the reading as CR or NCR.

Any measure that is, in the opinion of the investigator, abnormal AND CR must be recorded as history if found prior to the start of the first study medication application or as an AE if found after the start of the first study medication application.

6.2.4. Urine pregnancy tests

At Visits 1 and 7, the investigator or designee will perform a urine pregnancy test for subjects who are WOCBP. The urine pregnancy test kits used must have a minimum sensitivity of 25-mIU ß-HCG/milliliter (mL) of urine.

Subjects who are WOCBP must have a negative pregnancy test result at Visit 1 to continue in the study.

If the result of any post-treatment urine pregnancy test is positive, the subject will be withdrawn from the study and the subject's pregnancy documented and followed.

6.3. Other Evaluations

6.3.1. Demographics

At Visit 1, the investigator or designee will interview each subject to obtain demographic information including date of birth, sex at birth, race and ethnicity.

6.3.2. Medical history

At Visit 1, the investigator or designee will record medical history information including all medical conditions and disease states that:

- Are ongoing
- Require concomitant therapy
- Are, in the opinion of the investigator, relevant to the subject's study participation.

For women who are not of childbearing potential the reason they are not of childbearing potential must be reported as medical history.

6.3.3. Standardized photography

At Visits 2-7, an appropriately trained investigational center staff member other than the evaluating investigator will take standardized photographs to document the status of rosacea on the subject's face. The study images are intended to be used for scientific, training and promotional purposes.

Care must be taken to ensure similar lighting, background, subject positioning relative to the camera and camera settings are used for each photograph.

Equipment, supplies, training and detailed instructions for obtaining and managing the photographs will be provided to the investigational center prior to the initiation of subject enrollment.

Study photographs are to document the status of the subjects' clinical condition.

7. ADVERSE EVENTS

Adverse events will be monitored throughout the study and reported to Accuitis, Inc. on the appropriate AE CRF.

7.1. Definitions

7.1.1. Adverse events (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign or symptom associated with the use of an investigational product (including an abnormal laboratory finding), whether or not related to the investigational product.

Thus any new, clinically relevant worsening of an existing sign, symptom or disease, should be considered an AE.

Worsening of the Lesion Count, IGA or LTA should be reported as an AE only if the use of the study medication is interrupted or discontinued or other therapy is required to manage the event.

Every new episode or clinically relevant worsening of a chronic condition (*e.g.*, headaches, allergies, depression, and hypertension) should be reported as a separate AE, even if the condition is reported in the subject's medical history.

The investigator should, when certain, report a diagnosis rather than the signs, symptoms or clinically relevant abnormal laboratory values associated with the AE. Otherwise, signs, symptoms or abnormal laboratory values may be used to describe the AE.

An abnormality discovered (*e.g.*, clinically relevant laboratory abnormalities), prior to the first study medication application, should be reported as medical history, not as an AE.

7.1.2. Serious adverse event (SAE)

A Serious Adverse Event is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is an important medical event.

The term "life threatening" refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Inpatient hospitalization is considered to have occurred if the subject is admitted to the hospital on an in-patient basis even if released the same day. Prolongation of hospitalization is defined as an additional night stay in the hospital. Hospitalization for a diagnostic test (even if related to an AE) or elective hospitalization that was planned before study enrollment are not themselves reasons for an event to be defined as a SAE.

Important medical events are those that may not be immediately life threatening, result in death, hospitalization but are clearly of major clinical significance and may jeopardize the subject or require intervention to prevent one of the outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalization.

7.1.3. Unexpected adverse event

An unexpected AE is any AE that the investigator defines as related to a study medication, the nature of which is not consistent with the Investigator's Brochure or package insert.

7.1.4. Adverse event reporting period

AEs (serious and non-serious) must be reported starting with the subject's first study medication until the end of the subject's last study visit OR until 30 days after the subject's last study medication application, whichever is longer.

7.1.5. Severity

The investigator is to define the severity each AE using the following definitions as a guideline. The investigator will consider the range of the possible severity of the event and identify the severity that is the most appropriate according her/his medical judgment.

Mild – Awareness of signs or symptom, but easily tolerated

Moderate – Discomfort, enough to cause interference with usual activity

Severe – Incapacitating with inability to perform usual activity.

7.1.6. Relationship to study medication

The investigator will determine if there is a reasonable causal relationship between the study medication and an AE or not. The investigator will use her/his best medical judgment and consider all relevant factors (*e.g.*, temporal relationship, location of the event, the subject's relevant medical history, concomitant therapies and concurrent conditions) to determine the relationship of the AE to the study medication. The investigator will define the relationship of an AE to the study medication by selecting one of the following categories:

Related – There is a reasonable possibility that there is a causal relationship between the study medication and the AE.

Not Related – There is not a reasonable possibility that there is a causal relationship between the study medication and the AE.

The term "reasonable causal relationship" means there are facts or arguments to suggest a causal relationship (International Conference on Harmonization (ICH) E2A).

7.2. Reporting Procedures

7.2.1. Procedures for reporting adverse events

At each post enrollment visit, the investigator will question the subject to elicit AEs using a non-directive question such as "Has there been any change in your health since the previous study visit?"

Any AE noted during the reporting period must be reported in the source documents and on the appropriate AE CRF. AEs that are defined as "Not Related" to the study medications will be followed until they are resolved or until the subject's last visit. AEs that are defined as "Related" to the study medications will be followed until they are resolved or, if not resolved after the subject's last study visit, until in the opinion of the investigator, the AE reaches a clinically stable outcome with or without sequelae.

7.2.2. Procedure for reporting a serious adverse event

Upon becoming aware of a SAE occurring during the AE reporting period, whether or not related to the study medications, the investigator must:

1. Take the appropriate medical action to ensure the subject's safety
2. Immediately inform the Medical Monitor of the SAE by telephone:

3. Within 24-hours complete, as fully as possible, an AE CRF and an SAE form; fax or e-mail the forms and any other relevant information (*e.g.*, concomitant medication CRF, medical history CRF, laboratory test results) to the Accuitis, Inc. Medical Monitor.
4. Monitor and document the progress of the SAE until it resolves or, if not resolved after the subject's last study visit, until in the opinion of the investigator the AE reaches a clinically stable outcome with or without sequelae AND the investigator and Accuitis, Inc. Medical Monitor agree that the SAE is satisfactorily resolved.
5. Inform the Accuitis, Inc. Medical Monitor of SAE updates by telephone followed by an SAE form update sent by fax or by e-mail.
6. Comply with the appropriate regulatory requirements and Accuitis, Inc. instructions regarding reporting of the SAE to the responsible IRB.

8. PREGNANCY

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months). Even women who are using oral, implanted or injected contraceptive hormones, an intrauterine device, barrier methods (*e.g.*, diaphragm, condoms, spermicides) to prevent pregnancy, practicing abstinence or where the partner is sterile (*e.g.*, vasectomy) should be considered to be of childbearing potential.

All WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Effective methods of birth control approved for this study are:

- Implants (*e.g.*, Norplant® system); when used continuously for at least 90 days
- Injectables (*e.g.*, Depo-Provera®); when used continuously for at least 90 days
- Transdermal patch
- Combined oral contraceptives
- Barrier methods (*e.g.*, diaphragm, condoms with spermicides
- Intrauterine devices (*e.g.*, ParaGard® and Mirena®).

Abstinence or having a sterile partner is not considered an effective method of birth control.

Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion. During the trial, all WOCBP will be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period).

If a subject becomes pregnant during the study, or within 30 days of discontinuing the study medication, whichever is longer, the investigator should report the pregnancy to the Accuitis Inc. Medical Monitor within 24 hours of becoming aware of the pregnancy.

If a subject or investigator suspects that the subject may be pregnant prior to study medication administration, the study medication must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed, the subject must not receive study medication and must be discharged from the study.

If, following study medication administration, it is determined that the subject may have been or was pregnant at the time of study medication exposure the investigator must immediately notify the Accuitis Inc. Medical Monitor and record the event on a pregnancy surveillance form. All pregnancies must be reported using a pregnancy surveillance form and following the procedures for SAE reporting.
Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (*e.g.*, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the Accuitis, Inc. Medical Monitor on the pregnancy surveillance form, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of six weeks.

9. STATISTICAL ANALYSES

9.1. General Considerations

The statistical plan describes the statistical analysis as it is foreseen at the time of planning the trial. Any deviation from the statistical plan, the reasons for such deviations, and any additional statistical analyses that may be performed will be submitted as amendments prior to the unblinding of the randomization code.

All subject protocol deviations will be summarized in the clinical study report. All exclusions from the per-protocol population will be reviewed in a blind data review meeting before breaking the blind.

9.2. Types of Analyses (Intent-to-Treat, Per-Protocol)

The definitions of the populations for the different types of analyses follow those given in the ICH E9 guideline (1998).

9.2.1. Modified intention-to-treat analysis (MITT)

The modified intention-to-treat (MITT) population will include all randomized subjects who were dispensed study medication and provided any post-baseline efficacy data. The general analysis procedure for any post-baseline visit with missing efficacy data will be to impute data values from the most recent non-missing post-baseline visit. For analysis purposes, the endpoint analysis will use the last non-missing post-baseline data for each efficacy variable.

The safety population will include all randomized subjects. The analysis of safety will include variables such as clinical laboratory evaluations, vital signs, and adverse drug experiences. It is not necessary that measurements of any efficacy variable post randomization be available.

The MITT analysis provides estimates of treatment effects that may be more likely to mirror those effects observed in subsequent practice. Consequently, this analysis will be considered the primary efficacy analysis.

9.2.2. Per-protocol analysis (PP)

The per-protocol (PP) population is a subset of the MITT population and includes subjects who have no violations of the inclusion/exclusion criterion and who are compliant with treatment medication, defined as greater than or equal to 80% of specified medication. Before breaking the blind the precise reasons for excluding subjects from the PP population will be fully documented in a blinded data review meeting.

The last non-missing observation (post randomization) of these subjects will be carried forward to any subsequent missing visits and to endpoint.

9.3. Primary Efficacy Variable

9.3.1. Lesion count (papules, pustules and nodules)

Total lesion count is the sum of the papule count, the pustule count, and the nodule count. The total lesion count obtained at endpoint is the variable that will be used for the primary efficacy evaluation.

9.3.2. Statistical analysis of total lesion count

Total lesion count will be summarized for each treatment group and at each visit using mean, standard deviation, median, minimum, and maximum. The comparison between the two treatments will be based on the difference for each subject between each visit and Visit 2.

In accordance with ICH E9 guideline on Statistical Consideration in the Design of Clinical Trials (1998), the type 1 error rate of the test will be 5%.

At each post-baseline visit, an analysis of covariance (ANCOVA) will be performed to test the null hypothesis of no treatment effect. The dependent variable will be the difference between the value at each post-baseline visit, including endpoint, and the baseline value. The change from baseline to the endpoint (Visit 6) will be the primary efficacy analysis. The baseline value will be the covariate. Treatment group and study center will be the main effects in the model. This analysis will be performed on the MITT and PP populations. Efficacy will be declared if the treatment effect p-value for the MITT population is no greater than 0.05 and is favorable to ACU-D1 Ointment [redacted].

A second ANCOVA, which includes a treatment-by-center interaction, will be performed in order to test the significance of the interaction term in an exploratory manner. If the interaction term is significant at the 0.10 level, summary data will be presented for each study center in an appendix to the study report. In addition, if the interaction term is significant at the 0.10 level, the interaction term may be included in the final ANCOVA model to examine treatment effects if inclusion of this term increases the sensitivity of the analysis.
The residuals from the primary ANCOVA model will be analyzed for deviations from normality. If the test for normality fails at the 0.05 level of significance then the ANCOVA analysis will be supplemented by a Van Elteren test, stratified by study center.

Subgroup analyses including but not limited to race, age and gender will be performed for exploratory purposes, provided adequate sample sizes are available in potential subgroups. An exploratory mixed-model repeated-measures analysis of change from baseline across all post-baseline visits may be performed to explore changes in treatment effect over time and to potentially increase overall and by-visit sensitivity. Similar ANCOVA analyses to those described above will be performed on the PP population and will be considered exploratory analyses.

9.4. Secondary Efficacy Variables and Their Statistical Analyses

9.4.1. Investigator's global assessment

The Investigator's Global Assessment score is an ordered categorical value ranging from 0 (Clear) to 4 (Severe). The assessment is obtained at each visit.

Investigator's Global Assessment score will be summarized for each treatment group and at each visit using the median, minimum, maximum and frequency distributions. The comparison between the two treatments will be based on the difference for each subject between each visit, including the endpoint visit, and the baseline visit.

The van Elteren test, stratified by study center, as defined for the primary efficacy variable will be used for the analysis of IGA. Ordinal logistic regression models of the IGA, parameterized in the same manner as the ANCOVA models for the primary efficacy variable, will be used in an exploratory analysis of the impact of treatment on IGA scores.

9.4.2. Treatment responders

Treatment responders will be defined at each visit and at endpoint as subjects who have either (1) two ordinal or more reductions in the Investigator's Global Assessment (IGA) or (2) an IGA score of 0 or 1.

Treatment response (yes/no) is a dichotomous binomial variable. Treatment response will be summarized for each treatment group and at each visit using frequency distributions. At each visit, these scores will be analyzed using a Fisher's exact test supplemented by a Mantel-Haenszel analysis stratified by Investigator. The Breslow-Day test will be used to test the homogeneity of the treatment responder effect among investigators. The analysis of treatment success at endpoint visit is the primary responder analysis.

9.4.3. Individual lesion counts

As ancillary efficacy parameters, papules, pustule, and nodule counts will be summarized for each treatment group and at each visit using mean, standard deviation, median, minimum, and maximum. Change from baseline for papule, pustule, nodule, and papule plus pustule counts will be analyzed at each post randomization visit using the same parametric or non-parametric analysis as was used in the primary efficacy variable (total inflammatory lesions).

9.4.4. Subgroup analyses

Subgroup analyses including but not limited to race, age and sex will be performed for exploratory purposes on all secondary efficacy variables for the ITT population, provided adequate sample sizes are available in potential subgroups. In addition, the analyses performed on the PP population are considered exploratory.

9.5. Demographics and Baseline Characteristics

Demographic variables are race, age and sex. Age will be summarized for each treatment group using mean, standard deviation, median, minimum, and maximum. Gender and race will be summarized for each treatment group using frequency distributions.

Baseline characteristics are a complete medical history, lesion score (total number of facial lesions and number of papules, pustules, and nodules) and Investigator's Global Assessment score. Medical histories will be listed for each subject. Investigator's Global Assessment score will be summarized using frequency distributions and will be tested for baseline comparability of treatment groups using the Mantel-Haenszel Chi-Square test. Total number of facial lesions and numbers of papules, pustules, and nodules will be summarized for each treatment group using mean, standard deviation, median, minimum, and maximum and will be tested for baseline comparability of treatment groups using a two-sample Student's t-test.

9.6. Interim Analysis

No interim analyses will be conducted for this study.

9.7. Sample Size Determination

This is a pilot study for which no previous data are available to make a power calculation. This will be the seminal study.

10. TRAINING, MONITORING, DATA MANGEMENT, AND QUALITY ASSURANCE

10.1. Training

For each investigational center, there will be an initiation visit prior to enrolling any study subjects.

It is strongly recommended that all investigators, other evaluators, study nurses, study coordinators or other applicable personnel attend this visit. During this visit, participants will be trained to the protocol, study specific procedures, and the CRFs. Those unable to attend the initiation visit must receive on-site training prior to participating in any of the procedures and evaluations in this study.

Clinical Research Associates (CRAs) and other applicable personnel will be trained prior to study initiation to familiarize CRAs with the disease, the Standard Operating Procedures (SOPs), the protocol and other study specific items. Team organization, communication and operational issues will also be discussed.

Accuitis, Inc. will provide an investigational center file to each center.

10.2. Monitoring

The conduct of the study will be closely monitored by representatives of Accuitis, Inc. to verify adherence to ICH Good Clinical Practice (GCP) guidelines and applicable SOPs. Reports of these verifications will be archived with the study report. The investigator will allow the Accuitis, Inc. representatives designee and/or and any regulatory agency to have direct access to all study records, CRFs, corresponding subject medical records, study medication dispensing records and study medication storage area, and any other documents considered source documentation. The investigator also agrees to assist the representative, if required.

10.3. Data Management

Data-management activities of this study will be sub-contracted.

Edit checks and review processes will be performed by the sub-contractor until all data clarifications are resolved. The data will be exported to be stored in SAS datasets by the sub-contractor. After all data clarifications are resolved and subject's evaluability is determined, the database will be locked.

10.4. Quality Assurance

The study is conducted under the sponsorship of Accuitis, Inc. in compliance with the applicable regulatory requirements as well as applicable ICH guidelines, Helsinki Declaration and in respect of the Accuitis, Inc. and/or sub-contractor SOPs for study conduct and monitoring.

Audits may be carried out by the Accuitis, Inc. or the Accuitis, Inc. representatives and inspections may be performed by regulatory authorities or IRBs before, during or after the study. The investigator will provide the auditing/inspecting group direct access to all study records (*e.g.*, CRFs, subject medical records, study medication dispensing records) and the investigational center study facilities. The investigator and study staff will be available and will assist the auditing/inspecting groups as appropriate.

10.5. Changes in Study Conduct and Protocol Amendments

10.5.1. Study conduct and protocol amendments

With the exception of eliminating an immediate hazard to a subject, the investigator should not deviate from the protocol or implement any changes without prior written approval from Accuitis, Inc. and prior review and documented approval from the IRB.

Changes that involve only logistical or administrative changes are allowed. The investigator should document and explain any deviation from the protocol.

11. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

11.1. Institutional Review Board (IRB)

This protocol and all amendments, ICF and subject recruitment advertisements (if applicable) will be approved by an IRB.

11.2. Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, the ICH GCP guidelines, local regulatory requirements and, at US investigational centers, in compliance with the HIPAA.

11.3. Subject Information and Consent

All subjects who participate in this study must be fully informed about the study in accordance with the GCPs, federal regulations local regulations and, at US investigational centers, with HIPAA. The ICF, approved by an IRB, will be fully explained to the subject. Prior to any study related procedures, including washout from therapies, the subject will sign and date the ICF. The investigator must maintain each subject's ICF in the investigational center's study file and must provide each subject with a copy of the signed and dated ICF.

11.4. Contractual Requirements

A contractual agreement will be signed between Accuitis, Inc. and each investigator. This document will contain supplemental information, including financial terms, confidentiality, study schedule, third party responsibility, and publication rights.

11.5. Data Collection and Archiving

11.5.1. Data collection

The Investigator must maintain required records for all study subjects. Data for this study will be recorded in the subject's source document and on the CRFs. All data on these CRFs should be recorded completely and promptly. A copy of the completed CRFs for each subject will be retained by the investigational center.

11.5.2. Source documentation

Investigators must keep accurate separate records (other than the CRFs) of all subjects' visits that include all pertinent study related information. A statement should be made indicating that the subjects have been enrolled in this clinical study, and have provided written informed consent. Any AEs must be completely documented.

Source documentation includes results of any diagnostic tests conducted during the study.

11.5.3. Archiving

All pertinent data, samples, photographs, correspondence, original or amended protocol, reports and all other material relating to the study will be maintained securely by Accuitis, Inc./Contract Research Organization (CRO)/investigator archives for the legally required duration for archiving.

The investigator should maintain the essential study documents as specified in ICH GCP, and in compliance with all regulatory requirements. The investigator should ensure these documents are protected from accidental destruction or disposal.

If the Investigator needs to re-assign responsibility for maintaining these documents (*e.g.*, due to retirement) it must be transferred to a person willing to accept this responsibility. The investigator must notify Accuitis, Inc., in writing, of the name and address of the new individual.

12. REFERENCES

1 Wilkin JK. Rosacea: pathology and treatment. Arch Dermatol. 1994;130:359-362.