# STATISTICAL ANALYSIS PLAN

## FOR

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

**Protocol Number: ACU-DI-201 (Version 1.0 28-Jun-2017)**

**For**

**ACCUITIS, Inc.**

| Version | Date |
|---|---|
| 0.1 | May 11, 2018 |
| | |
| | |

Prepared by: _____
Date: ___/___/___
[redacted]

[redacted]

Approved by _____
Date: 6/7/2018
Rick Coulon
President
Accuitis

## TABLE OF CONTENTS

## 1. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| CSR | Clinical study report |
| MITT | Modified Intent-to-treat |
| ITT | Intent-to-treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mmHg | Millimeter of mercury |
| PP | Per protocol |
| PT | Preferred Term |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Standard deviation |
| SOC | System Organ Class |
| UPT | Urine pregnancy test |
| % | Percentage, number or ratio expressed as a fraction of 100 |

## 2. INTRODUCTION

The purpose of the statistical analysis plan (SAP) is to define the analysis for ACU-D1-201. The SAP should be finalized prior to database lock. Any deviations from the analyses described in the final SAP will be noted in the clinical study report (CSR).

## 3. 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.

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.

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. STUDY POPULATION

Approximately 36 subjects, male and female, 18 years of age or older who meet all the inclusion criteria and none of the exclusion criteria will be enrolled at two 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.

## 5. STUDY OBJECTIVE

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.

## 6. TRIAL 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.

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

The study will be conducted at two 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.

## 6.1. Endpoints

### *6.1.1. Efficacy Endpoints*

The primary efficacy evaluation is the total lesion count defined as the sum of the papule count, the pustule count, and the nodule count.

The secondary efficacy evaluations are:

- Investigator's Global Assessment score: an ordered categorical value ranging from 0 (Clear) to 4 (Severe)
- Treatment responders: 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

There is one ancillary efficacy evaluation of individual lesion counts: papules, pustule, and nodule counts.

### *6.1.2. Safety Endpoints*

Safety endpoints include:

- Adverse events
- Local tolerability of signs and symptoms of irritation
- Clinical laboratory safety tests
- Vital sign readings
- Urine pregnancy tests

### *6.1.3. Other Endpoints*

Standardized color photographs of the subject's face to document the status of the rosacea being treated will be taken throughout the study. No formal review of these is planned as part of this SAP.

### 6.2. Schedule of Observations

| 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

## 7. SELECTION AND WITHDRAWAL OF SUBJECTS

### 7.1. 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.

### 7.2. 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
8. Subject has facial hair, that in the investigator's opinion, might impair evaluation of rosacea or proper study medication application
9. Subject has a history of sensitivity to any of the ingredients in the study medications
10. Subject has participated in an investigational drug trial in which administration of an investigational study medication occurred within 30 days prior to Visit 1.

### 7.3. Subject Discontinuation

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.

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.

## 8. STATISTICAL 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.

Categorical variables will be summarized by the count (N) and percentage of subjects (%). Continuous variables will be summarized by the number of non-missing observations (N), mean, standard deviation (SD), median, minimum, and maximum values.

All study data will be displayed in the data listings.

## 8.1. Missing Values and Imputation

For both MITT and PP analyses, the last non-missing observation (post randomization) of these subjects will be carried forward to any subsequent missing visits and to endpoints.

For analysis purposes, the endpoint analysis will use the last non-missing post-baseline data for each efficacy variable.

## 8.2. Populations for Analysis

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.

### *8.2.1. 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 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.

### *8.2.2. Safety Population*

The safety population will include all randomized subjects who received at least 1 dose of study drug. 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.

### *8.2.3. 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.

## 8.3. Interim Analysis

No interim analyses are planned.

## 8.4. Subgroup Analysis

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

## 8.5. Baseline Characteristics

### *8.5.1. Definition of Baseline*

Baseline will be the data collected at Visit 2.

### *8.5.2. Demographic and Baseline Data*

Demographic data will be collected at the screening visit. The demographic data to be collected will include date of birth (age), sex at birth, race and ethnicity.

Subject demographic and baseline characteristics will be summarized for the MITT and PP set of subjects. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum and maximum), and categorical variables will be summarized using the count and percentage of subjects in each category.

Demographics will be provided in a subject listing.

### *8.5.3. Medical History*

The medical history data will be collected at the Visits 1 and 2.

Verbatim terms for Medical History will be mapped to their corresponding thesaurus terms (preferred term and system organ class) from the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, version 21.0. Summaries will be made using the assigned preferred terms, and will be based on the number and percentage of subjects having at least one occurrence

Analysis will include frequencies and proportions of patients reporting Medical History findings using the preferred terms and system organ class.

All conditions will be provided in a subject listing.

### *8.5.4. Medications*

Medication will be mapped to their corresponding ATC code from the WHO Drug Dictionary, version 2018. Summaries will be made using the Level 3 and 4 codes terms, and will be based on the number and percentage of subjects having at least one occurrence for all subjects in the Safety population.

Concomitant medications will be presented in a listing.

## 8.6. Subject Disposition

Subject disposition summary will include the number and percentage of subjects in each of the following categories:

- Subjects completing the study
- Subjects withdrawn early from study
- Reasons for discontinuation from study

Percentages will be based on the number of subjects randomized.

Subject disposition will be presented in a listing.

## 8.7. Study Visits

The number and percentage of subjects at each scheduled visit will be tabulated. By-subject data listing for visit participation will be prepared.

## 8.8. Protocol Deviations

The number and percentage of subjects who do not meet all of the inclusion and exclusion criteria will be tabulated by treatment group. The number and percentage of subjects who had a significant protocol deviation will be also tabulated.

By-subject listings of screen failures and protocol deviations will be prepared.

## 8.9. Extent of Exposure

Extent of exposure will be defined as the total ordinal number of days a subject is exposed to any study treatment. This will be calculated for each subject by taking the difference between the visit at which the first administration of study treatment took place and the date of last application. For subjects who are lost to follow-up, extent of exposure will be calculated based on the last study visit attended.

A summary of the number of days of exposure will be prepared for subjects in the Safety population.

The data for extent of exposure will be presented in a listing.

## 8.10. Compliance

Compliance will be assessed from subject daily diaries in which the number of applications will be captured. The overall percent compliant (<80% and ≥80%) will be tabulated for the MITT and PP populations and also compliance by visit will be summarized.

Compliance information will also be presented in a by-subject listing.

## 8.11. Efficacy Analyses

### *8.11.1. Primary Efficacy Variables: 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%.

Proc Mixed in SAS will be used to develop a repeated measures analysis of covariance (ANCOVA) model 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 endpoint. The baseline value will be the covariate. Treatment group and study center will be the main effects in the model. The mixed model will employ LOCF procedures for missing values. 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-DI 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 using Proc Npar1way in SAS, 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. Subgroups will be analyzed by adding the subgroup as a main effect and the interaction term of subgroup*treatment to the model.

### *8.11.2. Secondary Efficacy Variable: 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. Percent Change from baseline will be summarized for each follow-up visit. 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.

### *8.11.3. Secondary Efficacy Variable: 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.

### *8.11.4. Secondary Efficacy Variable: 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).

### *8.11.5. 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 MITT population, provided adequate sample sizes are available in potential subgroups. In addition, the analyses performed on the PP population are considered exploratory.

## 8.12. Safety Analyses

Safety analyses will be performed on the safety population. The assessment of safety will be based on the summary of AEs, clinical laboratory sampling local tolerability assessment and vital signs.

Safety assessments of continuous variables will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum and maximum), and categorical variables will be summarized using the count and percentage of subjects in each category.

### *8.12.1. Adverse Events*

Verbatim terms for AEs reported during the study will be mapped to their corresponding thesaurus terms (preferred term and system organ class) from the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, version 21.0. Summaries will be made

using the assigned preferred terms, and will be based on the number and percentage of subjects having at least one occurrence of the following:

- Any AE during the study;
- An AE within each system organ class;
- An individual AE (based on the preferred term).

Analysis will include frequencies and proportions of patients reporting AEs using the preferred terms and system organ class. Separate summaries of AEs with a suspected relationship to study medication (as reported by the Investigator) and by severity will be prepared. If applicable, the number of deaths and serious adverse events (SAEs) will also be presented, and events leading to discontinuation from the study will be listed and tabulated.

All AEs will be presented in a by-subject listing.

### *8.12.2. Local tolerability assessment (LTA)*

Investigator Assessment: Assessments will be tabulated by n (%) within each category at each applicable visit and timepoint.

Subject Assessment: Assessments will be tabulated by n (%) within each category at each applicable visit and timepoint.

The data on local tolerability will be presented in a listing.

### *8.12.3. Vital Signs*

At Visits 1, 2 and 7 vital signs to include 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) will be measured. The observed and change from baseline scores will be summarized using descriptive statistics. Height and weight will be presented in the Demography table, since they are measured only at Visit 1.

The vial sign data will be presented in a listing.

### *8.12.4. Clinical Laboratory Assessment*

At Visits 1 and 6 non-fasting blood samples will be collected for analysis including chemistry panel, complete blood count and urinalysis.

The clinical laboratory assessments will be presented in a listing.

### *8.12.5. Urine Pregnancy test*

The urine pregnancy tests will be presented in a listing.

## 9. LIST OF SUMMARY TABLES AND LISTINGS

Table shells and list of listings are in a separate document.