STATISTICAL ANALYSIS PLAN

Protocol Number:	DRM01B-ACN05
Study Title:	An Open-Label Study Assessing Long-Term Safety of Olumacostat Glasaretil Gel in Subjects with Acne Vulgaris
Development Phase of Study:	3
Sponsor:	Dermira, Inc.
Sponsor Contact:	Beth Zib
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Authored by:

SIGNATURE: Brian Armstrong DATE: 16 Apr 2018

Brian Armstrong, M.S.
Associate Director of Clinical Data Standards
QST Consultations, Ltd.

Reviewed by:

SIGNATURE: Laura Hatsis DATE: 12 APR 2018

Laura Hatsis, M.S.
Manager of Statistics
QST Consultations, Ltd.

Approved by:

SIGNATURE: DATE: 12 Apr 2018

Beth Zib
Clinical Lead
Dermira, Inc.

SIGNATURE: DATE: 11 APR 2018

Ramanan Gopalan, Ph.D.
Biostatistician
Dermira, Inc.

Revisions to the Statistical Analysis Plan described herein must be approved through a formal written amendment with the exception of minor editorial changes to tables, figures, or listing shells, and any necessary textual clarifications for programmers that do not affect the stated analysis variables, study endpoints, or statistical methods.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE(s)	adverse event(s)
BID	twice daily
DRM01B-ACN03	ACN03
DRM01B-ACN04	ACN04
DRM01B-ACN05	ACN05
ECG	electrocardiogram
eCRF(s)	electronic case report form(s)
ET	early termination
ICF	informed consent form
IGA	Investigator's global assessment
ITT	intent-to-treat
LSR(s)	local skin reaction(s)
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
QD	once daily
SAS®	Statistical Analysis System (SAS® Institute Inc., Cary, NC)
SOC	system organ class
TEAE(s)	treatment-emergent adverse event(s)

2. INTRODUCTION

Acne arises from a combination of physiological changes in the skin including altered sebaceous gland cell differentiation, heightened sebum production, localized bacterial colonization and inflammation. Although acne is generally viewed as a benign dermatological disease of adolescence, more severe forms may lead to permanent scar formation, with some of these patients suffering from psychological injury and significant loss of self-worth. Recent scientific advances in the understanding of the complex multi-factorial nature of this common disease offer great opportunity for scientific innovation through selective targeting of key elements of the disease process.

Topical agents routinely prescribed for acne, including antibiotics, retinoids and combinations thereof, often produce only modest therapeutic benefits and do not affect sebum production. A locally-delivered medication that selectively inhibited sebum formation would represent a breakthrough advance in reducing the pathogenic influences of sebum overproduction in acne.

Dermira, Inc. is pursuing the development of olumacostat glasaretil, previously referred to as DRM01B, a pro-drug of TOFA (5-(tetradecyloxy)-2-furancarboxylic acid), sarcosine ester, as a topically applied sebum inhibitor for the treatment of acne vulgaris. Olumacostat glasaretil is a

new chemical entity and has been formulated for clinical development as Olumacostat Glasaretil Gel, 5.0%.

The DRM01B-ACN05 (ACN05) study described herein is an open-label study to assess the long-term safety of continuous treatment with Olumacostat Glasaretil Gel, 5% for up to an additional 36-weeks in subjects who have completed either of the DRM01B-ACN03 (ACN03) or DRM01B-ACN04 (ACN04) studies.

3. STUDY OBJECTIVES

The objective of this study is to assess the long-term safety of Olumacostat Glasaretil Gel, 5.0%, in subjects with acne vulgaris.

This study may be stopped once at least 100 subjects have been treated for 36 weeks.

4. STUDY DESIGN

4.1 Overall Study Design

This study is an open-label, long-term safety study enrolling up to 700 subjects who participated in either ACN03 or ACN04 studies. All subjects will sign an informed consent / assent prior to continuing in this open label study.

Eligible subjects will receive open-label treatment with Olumacostat Glasaretil Gel, 5.0% and continue to dose twice daily for 36 weeks. Subjects, who participated in ACN03 study with acne on the chest, back or shoulders and applied study drug to affected areas will be allowed to continue to apply study drug to the affected areas. Subjects who participated in ACN04 study will continue to apply study drug to the face only. Subjects will receive a phone call at Week 2 to assess safety, and will return to the clinic at Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36 (End of Study).

Efficacy will be assessed via a static evaluation of qualitative overall acne severity, the investigator's global assessment of acne (IGA).

At the Week 12 and 24 visits, if the severity of acne has become worse, as determined by the IGA, the subject should be withdrawn, at the investigator's discretion. Severity of acne will be assessed on the face only.

Safety will be assessed through adverse events, local skin reactions (LSRs), serum chemistry, hematology and urinalysis laboratory testing, ECGs, physical examination, pulse and blood pressure.

Photographs of the face will be taken for all subjects in a subset of study sites in order to assess visually, the appearance of acne vulgaris during the course of the study.

During the clinic visit, subjects will be asked to complete the Acne Patient Self-Questionnaire.

4.1.1 Schedule of Visits and Assessments

The schedule of assessments can be found in Section 8 and Appendix 1 of the protocol.

4.1.2 Method of Assigning Subjects to Treatment Groups

Subjects will maintain the unique subject number assigned at randomization into their study of origin (either ACN03 or ACN04). All subjects will receive Olumacostat Glasaretil Gel, 5.0%, BID.

4.1.3 Blinding

This is an open-label study. Subjects will not be unblinded to their treatment assignment prior to enrollment into this study (ACN05). Once enrolled, each subject will receive Olumacostat Glasaretil Gel, 5.0%.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Efficacy Endpoint

The IGA of acne severity on the face only will be conducted for each subject every 12 weeks.

5.2 Safety Endpoints

Safety will be assessed through adverse events (AEs), local skin reactions (LSRs), serum chemistry, hematology and urinalysis laboratory testing, ECG testing, physical examination and vital signs.

6. STATISTICAL AND ANALYTICAL PLANS

6.1 General Methodology

All statistical processing will be performed using SAS® unless otherwise stated. Data will be summarized using descriptive statistics. No inferential testing or imputations for missing data will be performed.

Categorical variables will be tabulated with frequencies and percentages. Continuous variables will be tabulated with mean, median, SD, and range (minimum and maximum).

Reported AEs and prior and concomitant procedures and therapies will be classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Concomitant medications will be classified on the basis of World Health Organization Drug Dictionary (WHO-DDE) terminology.

The following data will be imported from ACN03/ACN04 (Baseline defined in section 6.1.2):

Subjects receiving Olumacostat Glasaretil Gel, 5.0% in ACN03/ACN04:

- Demographic information: age, gender, race and ethnicity
- Prior and Concomitant medications
- Adverse events
- Local skin reactions (Baseline and Weeks 4, 8, 12)
- Vital signs and weight (Baseline and Weeks 4, 8, 12)
- Investigator Global Assessment of acne (Baseline and Week 12)
- Acne Patient Self-Questionnaire (Baseline and Week 12)
- Laboratory evaluations: hematology, serum chemistries and urinalysis (Baseline)
- 12-lead ECG (Baseline)

Subjects receiving Olumacostat Glasaretil Gel, Vehicle in ACN03/ACN04:

- Demographic information: age, gender, race, and ethnicity
- Prior and Concomitant medications
- Adverse events
- Local skin reactions (Baseline)
- Vital signs and weight (Baseline)
- Investigator Global Assessment of acne (Baseline)
- Acne Patient Self-Questionnaire (Baseline)
- Laboratory evaluations: hematology, serum chemistries and urinalysis (Baseline)
- 12-lead ECG (Baseline)

6.1.1 Statistical Analysis

All analyses will be performed by QST using SAS® Version 9.3 or later. All summary tables and data listings will be prepared utilizing SAS® software.

The standard operating procedures (SOPs) of QST will be followed in the creation and quality control of all data displays and analyses.

6.1.2 Baseline Definition

The baseline value for each parameter will be defined as the last observation prior to first dose of Olumacostat Glasaretil Gel, 5.0%. For subjects receiving Olumacostat Glasaretil Gel, 5.0% in ACN03/ACN04, the baseline values from ACN03/ACN04 will be considered the baseline values for calculations in ACN05. For subjects receiving Olumacostat Glasaretil Gel, Vehicle in ACN03/ACN04, baseline values will most commonly be from the Week 12/study exit visit of ACN03/ACN04. If subjects choose to enroll in this study, study procedures will not be repeated; study sites will carry over the information from the ACN03/ACN04 study to the Day 1 visit for this study.

6.1.3 Visit Windowing

For subjects receiving Olumacostat Glasaretil Gel, 5.0% in ACN03/ACN04, data from ACN03/ACN04 will be included in summaries of ACN05. For subjects receiving Olumacostat Glasaretil Gel, Vehicle in ACN03/ACN04, baseline values will be sourced from ACN03/ACN04 and data from follow-up visits of ACN05 will be used in summaries. The table below details the analysis visits to be summarized and the associated visits from ACN03/ACN04 or ACN05 which will be sourced for each type of subject.

Analysis Visits for Efficacy and Safety Assessments

Analysis Visit	Subjects Receiving Olumacostat Glasaretil Gel, 5.0% in ACN03/ACN04	Subjects Receiving Olumacostat Glasaretil Gel, Vehicle in ACN03/ACN04
Week 4	ACN03/ACN04 - Week 4	ACN05 - Week 4
Week 8	ACN03/ACN04 - Week 8	ACN05 - Week 8
Week 12	ACN03/ACN04 - Week 12	ACN05 - Week 12
Week 16	ACN05 - Week 4	ACN05 - Week 16
Week 20	ACN05 - Week 8	ACN05 - Week 20
Week 24	ACN05 - Week 12	ACN05 - Week 24
Week 28	ACN05 - Week 16	ACN05 - Week 28
Week 32	ACN05 - Week 20	ACN05 - Week 32
Week 36	ACN05 - Week 24	ACN05 - Week 36
Week 40	ACN05 - Week 28	Not available
Week 44	ACN05 - Week 32	Not available
Week 48	ACN05 - Week 36	Not available

Note: analysis visits from ACN03/ACN04 will be utilized.

Data from ACN05 will be mapped to the appropriate analysis visit described above based on nominal visit indications. The nominal visit for vital sign and LSR data from early termination (ET) and unscheduled visits will be determined using nominal visit windows. The nominal visit windows for ET and unscheduled visits are presented in the following table.

ACN05 Nominal Visit Windows for Efficacy and Safety Assessments

Nominal Visit	Target Study Day	Window (Days)
Week 4	29	22 to 42
Week 8	57	43 to 70
Week 12	85	71 to 98
Week 16	113	99 to 126
Week 20	141	127 to 154
Week 24	169	155 to 182
Week 28	197	183 to 210
Week 32	225	211 to 238
Week 36	253	239 to 266

Data collected at ET and unscheduled visits prior to study day 22 will not be analyzed. Data collected at ET and unscheduled visits after study day 266 will not be included in analyses.

The definition for the study day included in each study window is defined as below:

Study Day prior to Day 1 = Visit Date – Day 1 Date

Study Day on or after Day 1 = Visit Date – Day 1 Date + 1

If an assessment's mapped nominal visit is a visit at which the subject has data from a scheduled visit present, or if no analyses are planned for the assessment at the mapped nominal visit, the data collected at the ET or unscheduled visit will not be included in analyses.

In the event of multiple values from unscheduled or ET assessments within a nominal visit window, the value closest to the scheduled visit target study day will be used for analyses. If two values tie as closest to the time point (for example, one value is before and the other value is after the time point), then the later value will be selected.

Other data summaries will include information collected at ET visits as Week 36/ET.

Data collected at all visits will be included in the data listings with the ACN05 analysis visit presented.

6.1.4 Adjustments for Covariates

Not applicable to this study.

6.1.5 Handling of Dropouts or Missing Data

No imputations for missing data will be performed.

6.1.6 Multicenter Studies

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling all the data for analysis. Every effort will be made to promote consistency in study execution at each study site.

6.1.7 Examination of Subgroups

As applicable, data will be summarized in total and by treatment received in ACN03/ACN04.

6.2 Disposition of Subjects

The number of subjects included in the safety population will be summarized for all subjects, for subjects that received Olumacostat Glasaretil Gel, 5.0% in ACN03/ACN04, and for subjects that received Olumacostat Glasaretil Gel, Vehicle in ACN03/ACN04. The number of subjects enrolled, completed, and discontinued (including the reasons for discontinuation) will be summarized similarly.

Subjects who are excluded from the safety population will be summarized by the reasons for exclusion.

6.3 Protocol Deviations

Protocol deviations will not be entered into the database. Deviations will not be programmed or summarized.

6.4 Data Sets Analyzed

6.4.1 Safety Population

All subjects who receive at least one confirmed dose of Olumacostat Glasaretil Gel, 5.0% and have at least one post-baseline (where baseline is the day that the subject received their first study drug) assessment will be included in the Safety Population. All analyses (efficacy and safety) will be performed using the Safety Population.

6.5 Demographic and Other Baseline Characteristics

All baseline summaries will be done on the safety population.

Sex, race, and ethnicity will be summarized by counts and percentages. Age will be summarized with descriptive statistics.

Age will be carried over from ACN03/ACN04 for those subjects who have the complete date of birth entered into the eCRF.

6.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded to preferred name and anatomical therapeutic chemical (ATC) classification of ingredients using the WHO-DDE.

Counts and percentages will be provided to summarize the use of prior and concomitant medications other than the study drug reported throughout the study. The number and percent of subjects reporting medications will be summarized by ATC level 2 term and preferred name. Ongoing medications and medications ending after the date of first application of Olumacostat Glasaretil Gel, 5.0% (from ACN03/ACN04 or ACN05) will be considered concomitant medications. Incomplete start and end dates which could be prior to first dose or after first dose will be considered prior to first dose.

A by-subject listing of all concomitant medications will be presented.

6.7 Analysis of Efficacy

6.7.1 Primary Efficacy Analysis

IGA will be summarized with frequency and percent distributions at baseline and final visit (Week 36/ET). The change in IGA level from Baseline to Week 36 will be summarized for the safety population in total, as well as by treatment received in ACN03/ACN04.

A by-subject listing of all IGA results will be presented.

6.7.2 Other Supportive Efficacy Analyses

IGA Scores and Acne Patient Self-Questionnaire assessments will be summarized by visit. Summaries of the frequency and percent distributions of the IGA Scores will be presented and descriptive statistics will be used to summarize the Acne Patient Self-Questionnaire. Satisfaction questions will be summarized with frequency and percent distributions. IGA Scores will be summarized by visit for all subjects as well as by treatment received in ACN03/ACN04.

For subjects receiving Olumacostat Glasaretil Gel, 5.0% in ACN03/ACN04, summary visits will include Baseline and Weeks 12, 24, 36 and 48. For subjects receiving Olumacostat Glasaretil Gel, Vehicle in ACN03/ACN04, summary visits will include Baseline and Weeks 12, 24, and 36.

6.8 Safety Evaluation

6.8.1 Extent of Exposure

The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of applications, number of missed applications, amount of study drug used, amount of study drug per day, percent compliance and number and percentage of subjects who are compliant. A subject will be considered compliant with the dosing regimen if the subject applied 80-120% of the expected number of applications while enrolled in the study.

For subjects receiving Olumacostat Glasaretil Gel, 5.0% in ACN03/ACN04, the date of first application will be from ACN03/ACN04. For subjects receiving Olumacostat Glasaretil Gel, Vehicle in ACN03/ACN04, the date of first application will be from ACN05.

Total number of days of exposure will be computed as follows:

Total Exposure = Date of Last Application – Date of First Application + 1.

Dosing deviations reported for areas other than the face will not be considered in calculations. On the date of first application and the date of last application, some subjects were to apply one dose and others were to apply two doses, depending on the time of the study visit. After the date of first application and before the date of last application subjects were expected to apply two doses. Missed applications will be calculated from dosing deviations which report zero or one application on a given date. Extra doses will be calculated from dosing deviations which report more than the expected number of applications on a given date.

For subjects receiving Olumacostat Glasaretil Gel, 5.0% in ACN03/ACN04, the total number of applications will be the sum of the applications from ACN03/ACN04 and ACN05, as dosing deviations are specific to the dates of first and last application within each study. The methodology below will be applied to ACN03/ACN04 and ACN05 data separately, then summed.

The total number of applications will be calculated as follows:

If the Date of First Application is not equal to Date of Last Application, then

Total Applications = 2*(Date of Last Application – Date of First Application – 1)

+ Expected Applications on Date of First Application

+ Expected Applications on Date of Last Application

– Missed Applications + Extra Applications.

If the Date of First Application = Date of Last Application, then

Total Applications = Expected Applications on Date of First Application

– Missed Applications + Extra Applications.

Treatment compliance will be based on the expected number of doses given the treatment period duration. Treatment period duration will be computed from the date of first application of Olumacostat Glasaretil Gel, 5.0% (from ACN03/ACN04 or ACN05) and the date of last application.

Then treatment period duration may be calculated as:

Treatment Period Duration = Date of Last Application – Date of First Application + 1.

Missed applications due to treatment-related AEs will be considered when determining the expected number of doses for each subject. If a treatment-related AE (regardless of location) requires interruption of study drug during the treatment period, missed applications during the AE (onset date to resolution date) will be deducted from the expected number of doses. Therefore, the expected number of applications will be calculated as:

Expected Applications = 2*(Treatment Period Duration – 2)

+ Expected Applications on Date of First Application

+ Expected Applications on Date of Last Application

– Applications Missed Due to a Treatment-Related AE.

Percent compliance will be calculated from total number of applications and total number of expected applications as follows:

Percent Compliance = 100*(Total Applications/Expected Applications).

Percent compliance will not be calculated for subjects who are lost to follow-up.

6.8.2 Adverse Events

AEs from ACN03/ACN04 will be included in the analysis for study ACN05. All AEs will be classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AEs (TEAEs) are defined as AEs with an onset on or after the date of the first application of Olumacostat Glasaretil Gel, 5.0% (from ACN03/ACN04 or ACN05). If treatment-emergent status cannot be determined (e.g., unknown date of first application), the AE will be considered treatment-emergent. AEs noted prior to the first study drug administration that worsen after baseline will also be reported as AEs and included in the summaries.

TEAEs will be summarized in total as well as by 12-week periods based on time of onset in relation to date of first application of Olumacostat Glasaretil Gel, 5.0%, based on the definitions below.

- 0-12 Weeks 0 <= onset day <= 85
- >12-24 Weeks 86 <= onset day <= 169
- >24-36 Weeks 170 <= onset day <= 253
- >36 Weeks onset day >= 254

Summaries will present the number of subjects reporting a TEAE by system organ class (SOC), preferred term, severity, relationship to study drug (causality), and seriousness. When summarizing TEAEs by severity and relationship, each subject will be counted once within a SOC or a preferred term by using the event with the greatest relationship or highest severity within each classification.

All information pertaining to an AE noted during the study will be listed by subject, detailing verbatim term given by the PI or designee, preferred term, SOC), onset date, resolution date, severity, seriousness, action taken, outcome and drug relatedness. The event onset will also be shown relative (in number of days) to date of first application.

Serious AEs (SAEs) will be summarized and listed using the same methodology as noted above. In addition, a listing of subjects who prematurely discontinue from the study due to an AE will be provided.

6.8.3 Clinical Laboratory Evaluation

Laboratory data will be presented in a by-subject listing. Any clinically significant laboratory abnormalities will be captured as adverse events. Changes from Baseline in safety laboratory values will be summarized at the final follow-up evaluation using descriptive statistics for the safety population in total, as well as by treatment received in ACN03/ACN04. For subjects receiving Olumacostat Glasaretil Gel, 5.0% in ACN03/ACN04, the final follow-up analysis visit will be Week 48/ET. For subjects receiving Olumacostat Glasaretil Gel, Vehicle in ACN03/ACN04, the final follow-up analysis visit will be Week 36/ET.

Additionally, changes from Baseline in safety laboratory values will be summarized using shift tables according to normal ranges.

If repeat laboratory testing was performed to follow-up on original results, summaries will be based on original results for each visit. If repeat laboratory testing was performed due to unavailable original test results (e.g., poor sample quality, insufficient amounts, etc.) summaries will be based on repeat results for each visit.

6.8.4 Other Observations Related to Safety

6.8.4.1 ECG Measurements

ECG data will be summarized at the final follow-up evaluation using descriptive statistics for the safety population in total, as well as by treatment received in ACN03/ACN04. Descriptive statistics will be provided for the following ECG parameters, for observed values and changes

from Baseline: heart rate (HR), RR duration, QRS duration, PR duration, QT duration and QTc duration. Change from Baseline in ECG abnormalities will also be summarized using shift tables at the final evaluation visit.

Shift tables will be based on the following categories:

- PR Interval: < 100 msec, 100 – 220 msec and > 220 msec;
- QRS Interval: < 50 msec, 50 – 110 msec and > 110 msec;
- QTcF Interval: < 450 msec, 450 – 500 msec and > 500 msec.

For subjects receiving Olumacostat Glasaretil Gel, 5.0% in ACN03/ACN04, the final follow-up analysis visit will be Week 48/ET. For subjects receiving Olumacostat Glasaretil Gel, Vehicle in ACN03/ACN04, the final follow-up analysis visit will be Week 36/ET.

6.8.4.2 Vital Signs

Vital signs will be presented by analysis visit as observed values and changes from Baseline using descriptive statistics. Specifically, analysis visits to be summarized include Baseline and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.

6.8.4.3 Physical Examination

Physical examination data will be presented in a by-subject listing.

6.8.4.4 Local Skin Reactions (LSRs)

Local Skin Responses (LSRs) include erythema, peeling, dryness, burning/stinging and pruritus. These will be scored as 0 (None), 1 (Mild), 2 (Moderate) or 3 (Severe). LSRs will be summarized by analysis visit using descriptive statistics. Specifically, analysis visits to be summarized include Baseline and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48. Each subject's worst post-baseline grade for each LSR will also be summarized. Additionally, the number of subjects who experience mild, moderate or severe LSRs post-baseline will be presented. By-subject listings of all LSRs, as well as subjects with any severe LSRs will be included.

7. DETERMINATION OF SAMPLE SIZE

The sample size for this study was based on the minimum requirement for a long-term safety study.

8. CHANGES IN THE PLANNED ANALYSES

No changes to planned analyses.