Advanced Clinical

Statistical Analysis Plan Approval Form

Client:	Galderma Laboratories, LP	
Identifier (e.g., Protocol Name and Number, ISS, ISE, SCS, or CSE):	GLI.04.SPR.US10355	
Version (Protocol Only):	☐ Original, Date:	☒ Amendment, Number 1; Date: 14SEP2016
Title:	EFFICACY AND SAFETY OF ADAPALENE 0.3% / BENZOYL PEROXIDE 2.5% GEL PLUS DOXYCYCLINE IN SEVERE INFLAMMATORY ACNE (NON-NODULOCYSTIC) SUBJECTS	
Statistical Analysis Plan Version:	☒ Original, Date: 30NOV2016	☐ Amendment, Number ; Date:

AC Statistical Analysis Plan Author:

Printed Name & Title

Handwritten Signature **OR** *Electronic Signature*

Signature: _____

Date: _____ (dd/mmm/yyyy)

Right-click to sign with CoSign

AC Statistical Analysis Plan Reviewer:

Printed Name & Title

Handwritten Signature **OR** *Electronic Signature*

Signature: _____

Date: _____ (dd/mmm/yyyy)

Right-click to sign with CoSign

First Client Statistical Analysis Plan Approval:

PPD Medical Director, RX

Printed Name & Title

Handwritten Signature

Signature: PPD Date: PPD (dd/mmm/yyyy)

Second Client Statistical Analysis Plan Approval ☐ Not Applicable

PPD

Printed Name & Title

Handwritten Signature

Signatur PPD Date: PPD (dd/mmm/yyyy)

ical Analysis Plan Approval ☐ Not Applicable

PPD

Printed Name & Title

itten Signature

Signature PPD Date: PPD (dd/mmm/yyyy)

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Effective 16NOV2016

Advanced Clinical

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Reason: Author

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Second Client Statistical Analysis Plan Approval ☐ Not Applicable

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Signature: _____ Date: _____ (dd/mmm/yyyy)

Third Client Statistical Analysis Plan Approval ☐ Not Applicable

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Signature: _____ Date: _____ (dd/mmm/yyyy)

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Galderma Laboratories, LP

STATISTICAL ANALYSIS PLAN
Protocol Number GLI.04.SPR.US10355

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EFFICACY AND SAFETY OF ADAPALENE 0.3% / BENZOYL PEROXIDE 2.5% GEL PLUS DOXYCYCLINE IN SEVERE INFLAMMATORY ACNE (NON-NODULOCYSTIC) SUBJECTS

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Final
30NOV016

Prepared By: Advanced Clinical LLC

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Table of Contents

Tables

List of Abbreviations and Definition of Terms

Abbreviation	Description
AE	Adverse Event
ATC-2	Anatomical Therapeutic Chemical 2nd level
ATC-3	Anatomical Therapeutic Chemical 3rd level
BMI	Body Mass Index
BP	Blood Pressure
BPO	Benzoyl Peroxide (C14H10O4)
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CCI	[redacted]
eCRF	Electronic Case Report Form
e.g.	For Example (Latin: *exempli gratia*)
eCTD	Electronic Common Technical Document
ET	Early Termination
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
ITT	Intent-To-Treat
LOCF	Last Observation Carried Forward
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SPF	Sun Protection Factor
UPT	Urine Pregnancy Test
US	United States
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes the efficacy and safety summaries and analyses that will be performed for Study GLI.04.SPR.US10355 (ALAMO), based on the study protocol Amendment 1 dated 14SEP2016.

A pharmaco-economic analysis will be described in a separate plan.

2 Overall Study Design and Objectives

2.1.1 Study Objectives

The clinical trial objective is to demonstrate that a daily treatment regimen of adapalene 0.3% / benzoyl peroxide 2.5% gel + oral doxycycline 200 mg is an effective and safe alternative to oral isotretinoin in subjects 12 years of age and older having severe inflammatory acne with ≤ 4 nodules/cysts > 1 cm in diameter (non-nodulocystic) during a 12-week treatment period.

2.1.2 Clinical Hypothesis

The proposed clinical efficacy hypothesis is based on the current Acne Treatment Guidelines for severe inflammatory acne from the American Academy of Dermatology/American Academy of Dermatology Association.

According to these Guidelines, first-line therapy for severe inflammatory acne is an oral antibiotic + topical combination therapy consisting of Benzoyl Peroxide (BPO) + Antibiotic *or* Retinoid + BPO *or* Retinoid + BPO + Antibiotic. Thus, daily combination therapy with adapalene 0.3% / benzoyl peroxide 2.5% gel and doxycycline 200 mg is a recommended first-line therapy for severe inflammatory acne; the hypothesis of this study is that this combination is an effective therapy alternative for oral isotretinoin.

2.2 Trial Design and Study Procedures

This is a Phase 4, 12-week, single-arm, open-label, multi-center investigational study in subjects with severe inflammatory acne.

This study will enroll male and female subjects, 12 years of age or older, presenting with severe inflammatory facial acne vulgaris with up to 4 nodules/cysts > 1cm in diameter on the face and a score of 4 (severe) on the Investigator's Global Assessment (IGA) scale, and who are, in the opinion of the Investigator, candidates for oral isotretinoin. If, at screening, the inclusion/exclusion criteria regarding the IGA score and nodule counts are not met, the subject should be screen-failed and will not complete a baseline evaluation. Rescreening will not be allowed during the trial.

Up to 40 independent study centers will participate in the study, and approximately 180 subjects will be enrolled. Subjects who meet the inclusion criteria and none of the exclusion criteria at the Screening visit will return to the clinic on Week 0 for baseline

measures and to start treatment, which will continue for a period of up to 12 weeks. Those screened subjects who do not need to undergo a wash-out period may combine the Screening and Baseline visits, and thus attend 4 clinic visits. Screened subjects requiring a wash-out period (up to 4 weeks) prior to baseline measurements and beginning treatment will attend a total of 5 clinic visits. Following the Baseline (Week 0) visit, all subjects will report to the clinic for efficacy and safety evaluations at Week 4, Week 8, and Week 12/ET.

Investigator Global Assessments (IGAs), Oral Isotretinoin Evaluations, and Local Tolerability Evaluations for a given subject are to be performed by the same Investigator (a Board-Certified Dermatologist) at all visits throughout the study, from Week 0 through Week 12/Early Termination (ET). Lesion Counts may be performed by a Board-Certified Dermatologist or a licensed Sub-Investigator (i.e., PA, NP, or RN) trained in the protocol, with the same evaluator performing the counts for a given subject at all visits throughout the study.

A urine pregnancy test (UPT) will be required at the Screening, Baseline, Week 4, Week 8, and Week 12/ET visits for all females of childbearing potential. The decision may be made by the Investigator to perform additional UPTs during the course of the study.

Subjects will be provided with Cetaphil Gentle Skin Cleanser and Cetaphil Daily Facial Moisturizer SPF 15 as needed during the study. To prevent dry skin, subjects will be requested to use a moisturizer throughout the study. If a subject experiences persistent dryness or irritation, the Investigator may consider a reduced application frequency for the investigational study drug gel, as required for the symptomatic relief of skin dryness or irritation.

A summary of the Study Schedule is provided in Table 1.

Table 1: Schedule of Assessments

PROCEDURES	Screening [h]	Week 0 (Baseline)	Week 4 (±3 days)	Week 8 (±3 days)	Week 12 [k] (±3 days)
Informed Consent with HIPAA / Assent (for minors)	X	X[i]			
Demographics / Medical History	X	X			
Previous Therapies and Medications [a]	X	X			
Concomitant Medications / Therapies / Procedures	X	X	X	X	X
Inclusion / Exclusion Criteria	X	X			
Urine Pregnancy Test	X	X	X	X	X
Lesion Counts [b,l]		X	X	X	X
Investigator Global Assessment [c,l]	X	X	X	X	X
Oral Isotretinoin Evaluation [l]	X	X	X	X	X
Local Tolerability [d,l]		X[j]	X	X	X
Adverse Events [e]		X	X	X	X
Subject Satisfaction Questionnaire					X
Subject Assessment of Acne Improvement					X
Acne QoL [f]		X			X
CCI					
Photographs		X	X		X
Study Treatments Dispensed		X	X	X	
Study Treatments Returned			X	X	X
Exit Form					X

a Acne treatment for the previous 6 months and all other therapies for the previous 4 weeks. Therapy that continues after baseline should be recorded on the Concomitant Medication Form of the eCRF.
b Inflammatory lesion and non-inflammatory lesion counts.
c Assessment is to be conducted on the face only.
d The Investigator must record and grade the severity of the signs and record the assessment of symptoms of local tolerability (erythema, dryness, scaling, and stinging/burning) at each visit. A symptom which requires a dose modification or concomitant medications/therapy should be recorded as an AE.
e AE onsets after subject signature of the ICF should be recorded on the AE Form of the eCRF.
f Only for subjects aged 13 years or older at Informed Consent.

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h In the event a wash-out period is required, the visit with the original Informed Consent Form (ICF) signature will be considered to be the Screening visit; the Baseline visit is to be scheduled as appropriate after the wash-out period. If no wash-out period is necessary, the Baseline visit is to be performed immediately (on the same day) as the Screening visit.
i If Screening and Baseline visits are combined, the ICF does not have to be signed again.
j Stinging/burning at the Baseline visit is to be assessed as None (0).
k Week 12 visit procedures are to be performed for early termination/exit visit.
l Each of these 4 evaluations are to be performed for a given subject by the same Investigator (or designee) throughout the study.

2.3 Treatments and Assignment to Treatments

This is an open-label study. All subjects will receive the investigational study drug adapalene 0.3% / benzoyl peroxide 2.5% gel in 45 g pump bottles plus oral doxycycline 200 mg tablets in 120-count bottles during the course of the study.

The study drug gel should be applied to dry skin once daily for 12 weeks, at night after washing with Cetaphil Gentle Skin Cleanser (provided by the Sponsor). A pea-sized amount of adapalene 0.3% / benzoyl peroxide 2.5% gel should be put on the fingertip and applied to the forehead. The procedure is repeated with a pea-sized amount applied to each cheek and to the chin and nose, being careful to avoid application to the nostrils, mouth, lips, and eyelids. The objective is to cover the entire face with a thin film of the treatment, even if there are areas on the face that do not have acne. While there are five areas of the face to be treated (forehead, right cheek, left cheek, chin, and nose), four pea-sized amounts of the study drug are typically estimated to be enough for the entire face. The product should not be applied to cuts, abrasions, or eczematous or sunburned skin.

At the Baseline/Week 0 visit, each subject will receive two 120-count bottles of the investigational study drug doxycycline hyclate (50 mg tablets) and will be resupplied at each study visit (Week 4 and 8 only) with one new bottle. During the Baseline/Week 0 visit, subjects will be instructed to take the first 100-mg dose of doxycycline hyclate at the same time as the adapalene 0.3% / benzoyl peroxide 2.5% gel treatment that evening. They will take the second 100-mg dose the next morning. The subject will be instructed to completely use one bottle of doxycycline hyclate before starting a subsequent bottle. For the 200 mg per day dosing regimen, each subject will take two 50-mg tablets of doxycycline hyclate in the morning and at night, for a total of four tablets (a total of 200 mg) daily for 12 weeks. The tablets should be swallowed, not chewed, should be taken with adequate amounts of fluid, and may be taken with food.

Signs and symptoms of local tolerability are possible during treatment (erythema, scaling, dryness, and stinging/burning). To prevent dry skin, subjects will be requested to use a moisturizer (Cetaphil Daily Facial Moisturizer SPF15, provided by the Sponsor) throughout the study as needed. If a subject experiences persistent dryness or irritation, the Investigator may consider a reduced application frequency of the investigational study drug gel as required for the symptomatic relief of skin dryness or irritation.

Descriptions and use of the study medications, both the investigational drugs and the non-investigational products, are summarized in Table 2.

Table 2: Description and Dispensing of Study Medications

Investigational Study Drug:	**Adapalene 0.3% / Benzoyl Peroxide 2.5% Gel**
Form	Topical Emulsion (Gel)
Dose	Apply a thin film of adapalene 0.3% / benzoyl peroxide 2.5% gel to affected areas of the face once daily in the evening after washing. Use a pea-sized amount for each area of the face (e.g., forehead, right cheek, left cheek, chin, and nose). Avoid the eyes, lips, and mucous membranes.
Mode of Administration	Topical
Duration of Treatment	12 weeks
Quantity Supplied	1 bottle per visit (not Week 12/ET)
How Supplied	45 g bottle with pump
Storage and Handling	Store at 25°C. Excursions permitted to 15°C - 30°C. Protect from light and keep away from heat.
Investigational Study Drug:	**Doxycycline Hyclate**
Form	50 mg tablets
Dose	200 mg daily
Mode of Administration	Oral
Duration of Treatment	12 weeks
Quantity Supplied	2 bottles at Baseline, 1 bottle at each subsequent visit (not Week 12/ET)
How Supplied	120 tablets per bottle
Storage and Handling	Store at 25° C. Excursions permitted to 15°C – 30° C.
Non-Investigational Study Product:	**Cetaphil Gentle Cleanser**
Form	Viscous, slightly translucent, off-white lotion
Dose	Twice a day
Mode of Administration	Topical
Duration of Treatment	12 weeks
Quantity Supplied	1 bottle for duration of study, at Baseline visit
How Supplied	16 oz bottle
Storage and Handling	Room temperature
Non-Investigational Study Product:	**Cetaphil Daily Facial Moisturizer SPF 15**
Form	Lotion
Dose	As needed
Mode of Administration	Topical
Duration of Treatment	12 weeks
Quantity Supplied	1 bottle per visit (not Week 12/ET)
How Supplied	4 oz bottle
Storage and Handling	Room temperature (away from excessive heat and direct sun)

2.3.1 Dose Modification

If a subject experiences persistent dryness or irritation despite use of the moisturizers provided, the Investigator may consider dose modification; i.e., reducing the once-daily treatment regimen to every other day. The Investigator should attempt to return the subject to once-daily treatment within two weeks.

If this dose modification occurs between Baseline Week 0 and Week 4, and lasts more than 2 weeks after the onset date of the dryness or irritation, the signs or symptoms of local tolerability should be recorded as an AE. After the Week 4 visit, the signs or symptoms related to this dose modification should be recorded as an AE, regardless of the duration of the dose modification.

3 General Analysis Conventions

Data collected in this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum). Categorical variables will be summarized using counts and percentages for each response category. Confidence intervals (CI) will be presented as appropriate. All evaluations (including CIs) will be reported for explorative purposes and will be interpreted as such.

Study days will be calculated relative to the first dose of study drug. Day 1 will be the first day of study drug administration in the study, and the day prior to the first dose of study drug administration will be Day -1. There will be no Day 0.

Baseline will be the last assessment prior to the first dose of study drug unless otherwise indicated.

No formal statistical tests will be performed.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0. Prior and concomitant medications as well as prior and concomitant medical and surgical procedures will be coded using the World Health Organization (WHO) Drug Dictionary (March 2015).

Data for all subjects in the clinical database will be included in the data listings. Calculated (derived) variables will be listed as appropriate. Tables, listings, and figures will be programmed using SAS Version 9.3 or higher.

A list of proposed statistical tables and data listings is provided in Section 14.

Any changes from the SAP will be detailed in the clinical study report.

3.1 Study Periods

The study consists of a Screening wash-out period and a treatment period. Screened subjects visit the clinic on Week 0 for baseline measures and to start treatment. Those screened subjects who do not need to undergo a wash-out period may combine the Screening and Baseline visits, and thus attend 4 clinic visits. Screened subjects requiring a wash-out period (up to 4 weeks) prior to baseline measurements and beginning treatment will attend a total of 5 clinic visits. Following the Baseline (Week 0) visit, all subjects will report to the clinic for efficacy and safety evaluations at Week 4, Week 8, and Week 12/ET.

3.2 Visit Windows

Study visits are expected to occur according to the schedule outlined in the protocol. All data will be summarized based on the actual visit as recorded on the eCRF.

4 Analysis Populations

4.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population consists of the entire population enrolled at baseline. All efficacy data will be analyzed for the ITT population.

4.2 Safety Population

The Safety Population consists of the Intent-to-Treat population, after exclusion of subjects who never took the treatment with certainty, based on drug accountability data. All safety analyses will be summarized for the Safety Population.

5 Subject Disposition

Subject disposition will be summarized overall. The number of subjects in intent-to-treat and safety population will be summarized. The number and percentage of subjects in the ITT population who complete the study will be summarized, along with the number and percentage of subjects who do not complete the study for each discontinuation reason as specified on the eCRFs. Inclusion/exclusion data will be presented by subject in a data listing.

6 Protocol Deviations

Protocol deviations will be presented by subject in a data listing.

7 Demographic and Baseline Characteristics

7.1 Demographic Characteristics

Demographic and baseline characteristics at study entry will be summarized overall for the safety population. Variables to be summarized are:

- Continuous variables
  - Age (years)
  - Time since Acne Onset (months)
  - Inflammatory Lesion Count
  - Non-inflammatory Lesion Count
  - Total Lesion Count

- Categorical variables
  - Sex
  - Race
  - Ethnicity
  - Wash-Out Status (Yes, No)
  - Age Category (≤ 17, 18 – 24, >= 25 years)
  - Age at Acne Onset (≤ 11, 12 – 14, 15 – 17, >= 18 years)
  - Time since Acne Onset Category (based on quartiles in months)

Time since acne onset will be calculated as the informed consent date minus the onset date of acne vulgaris collected on medical history CRF expressed in months. If the day of acne onset date is missing, 15 will be imputed for calculations. If the acne onset month is missing the month and day of the informed consent date will be used for calculations. Similarly, age at acne onset will be calculated based on the onset date of acne vulgaris and the date of birth.

Continuous variables will be summarized with descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Categorical variables will be summarized using counts and percentages.

Demographic and baseline characteristics will be presented by subject in data listings.

7.2 Medical History

Medical history information will be presented by subject in a data listing.

8 Efficacy Assessments

8.1 Lesion Counts

The primary efficacy endpoint is the reduction in the number of inflammatory lesions at Week 12/ET. Lesion counts will be performed by the Investigator at baseline and each post-baseline visit. Each type of lesion will be counted separately and recorded on the appropriate eCRF page. The lesion counts will be taken from the forehead, right cheek, left cheek, chin, and nose.

The following lesion types will be counted:

- Inflammatory Lesions
  - Papule – a small, red, solid elevation equal to or less than 0.5 cm in diameter.
  - Pustule – a small, circumscribed elevation of the skin that contains yellow-white exudate.
- Non-inflammatory Lesions
  - Open Comedone – a pigmented dilated pilosebaceous orifice (blackhead).
  - Closed Comedone – a tiny white papule (whitehead).

The inflammatory lesion count is the sum of the number of papules and pustules over all regions of the face, and the non-inflammatory lesion count is the sum of the open and closed comedones over all regions of the face.

8.2 Investigator's Global Assessment (IGA)

A Board Certified Dermatologist will assess the subject's acne severity using the IGA scale at every visit, performing a static ("snap-shot") evaluation of acne severity. No reference to baseline or other previous visits should be made by the Investigator when evaluating the subject's facial acne. The IGA is dichotomized, such that Success is clearly defined as 0=Clear and 1=Almost Clear.

The IGA Severity Scale is presented in Table 3.

Table 3: Investigator's Global Assessment Severity Scale

Severity Scale		Description
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the face is involved. Many comedones, papules and pustules. One small nodule may be present.
4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules may or may not be present.

8.3 Oral Isotretinoin Evaluation

At each study visit, subjects will be evaluated to determine if, in the opinion of the Investigator, they are still candidates for oral isotretinoin. Regardless of the results, subjects will not be exited from the study due to this evaluation, and will continue participation in the study.

8.4 Subject's Assessment of Acne Improvement

The Subject's Assessment of Acne Improvement on a 0 to 5 scale, as given in Table 4, will be documented at the Week 12/ET visit, based on a comparison to the subject's facial acne condition at Baseline.

Table 4: Subject's Assessment of Acne Improvement Scale

Severity Scale	Description
0	Complete Improvement
1	Marked Improvement
2	Moderate Improvement
3	Minimal Improvement
4	No Change
5	Worse

8.5 Subject Satisfaction Questionnaire

The Subject Satisfaction Questionnaire will be completed by the subject at Week 12/ET. The questionnaire has seven questions, most with four possible responses to assess the subject's satisfaction with study treatment, where a lower score represents higher satisfaction.

8.6 Acne-Specific Quality of Life Questionnaire (Acne-QoL)

The Acne-QoL will be collected at Baseline and the Week 12/ET visit. The Investigator or designee provides the subjects who are ages 13 and older at Informed Consent, with the Acne-QoL form and instruct the subject to read and answer all questions. Subjects who are 12 years of age at the time of Informed Consent will not complete this questionnaire.

The questionnaire will measure the impact of facial acne on health-related quality of life. There are 19 questions, with multiple-choice responses on a 0-6 scale, where higher scores represent a higher quality of life.

Questions are separated into 4 domains:

i) Self-perception (5 questions - total score range from 0 to 30)
ii) Role-emotional (5 questions - total score range from 0 to 30)
iii) Role-social (4 questions - total score range from 0 to 24)
iv) Acne symptoms (5 questions - total score range from 0 to 30)

The score for each domain is calculated by summing the score for the questions pertaining to the domain. At least 3 items must be answered within each domain in order to calculate the domain scores. If the minimum numbers of items have been answered but 1-2 questions have missing responses, the mean value is calculated within the domain for the answered items and missing values are replaced with the mean value. If fewer than the minimum number of items have been answered, the domain score should not be calculated.

Content areas for each domain (i.e., questions contributing to each domain) are given below:

Self Perception		**Role-emotional**	
1	Feel unattractive	5	Spending time treating face
3	Feel self-conscious	9	Need to have meds or cover-up available
10	Self-confidence affected	8	Meds won't clear face fast enough
2	Feel embarrassed	7	Not looking your best
6	Dissatisfied with self-appearance	4	Feel upset
Role-Social		**Acne Symptoms**	
12	Going out in public	15	Bumps on face
11	Meeting new people	16	Bumps full of pus
14	Interacting with opposite sex (or same sex if gay) a problem	17	Scabbing from acne
13	Socializing with people a problem	18	Concerned with scarring
		19	Oily skin

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9 Efficacy Analysis

All efficacy variables will be summarized at each scheduled visit for the ITT Population. Categorical variables will be summarized by counts and percentages for each response category (N, %). Continuous variables will be summarized using number of subjects, mean, SD, median, minimum, and maximum for the data collected at each visit, and for change from baseline to each visit where appropriate. CIs will be presented as appropriate. All evaluations (including CIs) will be reported for exploratory purposes and will be interpreted as such. No formal confirmatory statistical testing is planned in this trial.

9.1 Primary Efficacy Analysis

The primary endpoint is the reduction in the number of inflammatory lesions at Week 12/ET. The reduction in lesion count will be summarized with descriptive statistics. A 95% CI for the reduction in lesions will be presented. The data will be summarized as

observed, with no imputation for missing values. A last observation carried forward (LOCF) approach will be used as a sensitivity analysis.

9.2 Secondary Efficacy Analysis

Secondary efficacy endpoints are:

- IGA Success Rate at Weeks 4, 8, and 12/ET
- Percent reduction in total, inflammatory, and non-inflammatory lesions at Weeks 4, 8, and 12/ET
- Number and percent of subjects who, in the opinion of the Investigator, are candidates for oral isotretinoin at Weeks 0, 4, 8, and 12/ET
- Reduction in number of total, inflammatory, and non-inflammatory lesions at Weeks 4, 8, and 12/ET
- Subject Assessment of Acne Improvement at Week 12/ET

The IGA Success Rate is defined as the number and percent of subjects rated as Clear (Grade 0) or Almost Clear (Grade 1). It will be summarized at Weeks 4, 8, and 12/ET with a 95% CI for the Success Rate using Wilson's score method.

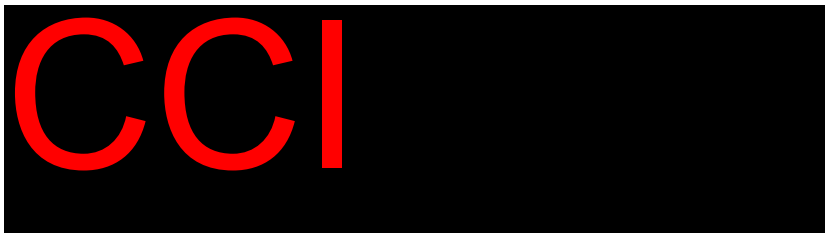
The reduction in lesion count (both percent and number of lesions) at Weeks 4, 8, and 12/ET will be summarized with descriptive statistics and a 95% CI for the reduction in lesions. The % reduction is calculated as 100% multiplied by (the lesion count at baseline minus the lesion count at each week divided by the lesion count at baseline).

The number and percent of subjects who are candidates for oral isotretinoin will be summarized at Weeks 0, 4, 8, and 12/ET, and a 95% CI will be provided using Wilson's score method. Subgroup analyses for the number and percent of subjects who are candidates for oral isotretinoin are described in Section 10.4.

The Subject Assessment of Acne Improvement at Week 12/ET will be summarized with counts and percentages for each category (ranging from 0 = Complete Improvement to 5 = Worse).

All data will be summarized as observed with no imputation for missing values. LOCF will be performed as a sensitivity analysis for IGA Success Rate, number of subjects eligible for oral isotretinoin, and lesion counts.

All efficacy data will be presented by subject in data listings.



10 Statistical/Analytical Issues

10.1 Handling of Dropouts or Missing Data

For analyses of the observed data, no imputation will be performed for missing values, except where specified. If any items of the Acne-QoL questionnaire are not answered, Section 8.6 describes rules how to replace the missing value and calculate domain score. A sensitivity analysis of the efficacy variables will be performed by applying lastobservation carried forward (LOCF) approach for the ITT population. For LOCF, the last post-baseline assessment will be carried forward. Early termination records will be summarized at Week 12 for subjects who prematurely discontinue.

10.2 Pooling of Centers in Multi-Center Studies

There will be no pooling of centers.

10.3 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be made since no formal statistical testing will be performed.

10.4 Examination of Subgroups

The number and percent of subjects who are candidates for oral isotretinoin at Week 12/ET will be summarized by applying both observed and LOCF approach for the ITT population for the following subgroups:

- Time since acne onset (based on quartiles in months) by gender
- Age of acne onset (≤ 11, 12 – 14, 15 – 17, >= 18 years) by gender

10.5 Interim Analysis and Data Monitoring

An interim analysis is planned for this study which will summarize data for all subjects who have completed the study by February of 2017 as outlined in the Interim Analyses Plan. All analyses described in this SAP will be provided for the interim analysis.

11 Safety Analysis

The safety endpoints include study drug exposure, adverse events, and local tolerability. All safety data will be included in the data listings. All safety data will be summarized as observed with descriptive statistics for the safety population.

11.1 Study Drug Exposure

The following variables will be summarized for both the Adapalene 0.3% / benzoyl peroxide 2.5% gel and doxycycline hyclate tablets using descriptive statistics:

- Duration of study drug exposure
- Adapalene 0.3% / benzoyl peroxide 2.5% average daily use (g/day)
- Compliance with doxycycline hyclate

Study drug exposure will be calculated as the duration from the date of first dose to the date of last dose as:

Exposure (days) = Last Dose Date – First Dose Date +1.

The average daily use for Adapalene 0.3% / benzoyl peroxide 2.5% gel will be based on the weight of the returned gel and will be calculated as amount of product used (in grams) divided by the exposure. Compliance for doxycycline will be based on the number of tablets dispensed and returned and will be calculated as number of tablets consumed (i.e. total number dispensed – total number returned) divided by the expected number of tablets taken. The expected number of tables taken is 4 x (last dose date – first dose date) + 2 (subjects are supposed to take 2 tablets the evening of their baseline visit, and 4 tablets daily during the rest of the treatment period).

Study drug administration and accountability data will be presented by subject in data listings.

11.2 Adverse Events

Adverse events (AEs) will be summarized for the safety population. All AEs will be coded using MedDRA and presented by MedDRA system organ class (SOC) and preferred term (PT). Any AE with onset or worsening of a pre-existing condition on or after the first dose of study drug through the end of participation in the study will be considered a treatment-emergent adverse event (TEAE).

Adverse events with partial dates will be assessed using the available date information to determine if treatment-emergent. Adverse events with a missing start date will be considered treatment-emergent unless the event has a stop date prior to the date of the first dose of study drug.

11.2.1 Overview of Treatment-Emergent Adverse Events

An overview summary of TEAEs will include the number and percentage of subjects in each of the following categories:

- Subjects reporting at least one TEAE
- Subjects reporting at least one treatment-related TEAE
- Subjects reporting at least one serious AE (SAE)
- Subjects reporting at least one TEAE leading to discontinuation of study drug
- Subjects with at least one AE resulting in death

11.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects with the following categories of TEAEs will be summarized by SOC and PT:

- Any TEAE
- Any TEAE by severity
- Any TEAE by relationship to study drug
- Any treatment-emergent SAE
- Any TEAE leading to discontinuation of study drug

The number and percentage of subjects who experienced at least one TEAE will be summarized overall and for each SOC and each PT. The percentage will be based on the number of subjects in the safety population. Each subject will contribute at most one count per summarization category. In other words, if a subject has more than one TEAE with same PT, the subject will be counted only once for that PT. Similarly, if a subject

has more than one TEAE for a SOC, the subject will be counted only once in that SOC and PT.

Adverse event severity is classified as mild, moderate, or severe. If a subject has multiple occurrences of the same system organ class or preferred term, then only the most severe event will be summarized in the tables for that system organ class and preferred term. Missing severity will be considered severe.

The relationship of the AE is classified into 2 categories of "Reasonable Possibility" and "No Reasonable Possibility". If a subject has multiple occurrences of the same system organ class or preferred term, then only the most related event will be summarized in the tables for that system organ class and preferred term. Missing relationships will be considered "Reasonable Possibility".

All reported AEs will be listed in data listings. By-subject listings also will be provided for all subjects (safety population) for the following: treatment-related AEs, AEs resulting in discontinuation of study drug, and serious AEs.

All AEs will be presented by subject in data listings.

11.3 Local Tolerability

Signs and symptoms of local tolerability (erythema, scaling, dryness, and/or stinging/burning) will be summarized for the safety population by frequency and percentage for each response category for baseline and each post-baseline visit. The local tolerability scores for each category, and the change from Baseline to each post-baseline visit, will also be summarized using descriptive statistics (number of subjects, means, medians, SDs, minimums, and maximums). A shift table will be prepared showing shift from baseline to worst on-treatment value for each symptom. Scores range from 0 = None to 3 = Severe, according to Table 5.

Table 5: Local Tolerability Severity Scale

Severity		**Description**
Erythema – abnormal redness of the skin		
0	None	No erythema
1	Mild	Slight pinkness present
2	Moderate	Definite redness, easily recognized
3	Severe	Intense redness
Scaling – abnormal shedding of the stratum corneum		
0	None	No scaling
1	Mild	Barely perceptible shedding, noticeable only on light scratching or rubbing
2	Moderate	Obvious but not profuse shedding
3	Severe	Heavy scale production
Dryness – brittle and/or tight sensation		
0	None	No dryness
1	Mild	Slight but definite roughness
2	Moderate	Moderate roughness

3	Severe	Marked roughness
Stinging/Burning – prickling pain sensation immediately after (within 5 minutes) dosing		
0	None	No stinging/burning
1	Mild	Slight warm, tingling/stinging sensation; not really bothersome
2	Moderate	Definite warm, tingling/stinging sensation that is somewhat bothersome
3	Severe	Hot, tingling/stinging sensation that has caused definite discomfort

Note: Stinging/Burning at the Baseline visit is to be assessed as none (0).

Local tolerability results will be presented by subject in a data listing.

11.4 Prior and Concomitant Medications

The number and percentage of the subjects who took each medication will be tabulated by WHO Drug Dictionary Anatomical Therapeutic Chemical 3rd level (ATC-3) and preferred name for concomitant medications. If the 3rd level term is not available, the next available level (e.g., ATC-2) will be used. A subject will only be counted once within each ATC-3 code and within each preferred name.

Medications will be included in the concomitant medication summary if they were taken on or after the first day of the study drug administration, regardless of when the medication started. Medications with partial dates will be assessed using the available date information to determine if they will be categorized as concomitant medications. If an end date is missing or the medication is ongoing, the medication will be included as concomitant.

Prior medications are defined as those ending prior to the first dose of investigational study drug.

All prior and concomitant medication data will be presented by subject in a data listing. All prior and concomitant medical and surgical procedures will be presented by subject in a data listing.

12 Quality Control

All data displays and analyses will adhere to the International Conference on Harmonisation (ICH) *Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3).*

All analyses will be performed using SAS® Version 9.3 (or later). Advanced Clinical will follow its standard operating procedures in the creation and quality control of all tables, listings, figures, and analyses. Galderma or its designee will review all tables, listings, and figures prior to final database lock. All final SAS programs and associated output files will be transferred to Galderma in agreed-upon format at project completion.

13 Tables and Listings Conventions

Mock-ups for statistical tables and listings will be provided. Final formats for the statistical tables and listings may deviate from these mock-ups upon agreement with Galderma. Footnotes will be used as needed to clarify the information that is presented in the tables and listings. Unless otherwise requested by Galderma, the term 'subject' will be used in all tables and listings, in accordance with Clinical Data Interchange Standards Consortium (CDISC) standards.

The general layout of tables and listings will be as follows:

Galderma Laboratories, LP
Protocol: GLI.04.SPR.US10355
Clinical Study Report

Page x of y
Run Date: DDMMMYY-HH:MM

Listing 16.2_x (or Table 14.x_x)

<Title>

<Population>

Col 1	Col 2	Col 3	etc

<Any footnotes>

File Name: <pathname for SAS program>

All tables and listings will use landscape orientation. Margins will be at least 2.0 cm at the top and bottom and at least 0.8 cm on the left and right, excluding headers and footers, in accordance with electronic Common Technical Documents (eCTD) guidelines. Font will be Courier New, unless otherwise specified, with a 10-point font size in most cases. Page numbering will be sequential within each table, listing, and figure. Column headers should be in initial capital letters. Units for numeric data will be included when appropriate.

Unless otherwise requested by Galderma, the derivation of relative study day will follow CDISC standards. The first day of study agent administration will be Day 1, with a negative sign indicating the number of days prior to the first day of study agent administration (e.g., Day -1 is the day prior to first administration of the study drug agent). There will be no Day 0.

Tables and data listings will be created from different SAS programs. A single program may produce multiple tables or multiple data listings from the same dataset (e.g., all clinical chemistry data listings may be generated by a single program).

Statistical Table Conventions

Mock-ups for statistical tables will include headers, title numbers, titles, column headers and footers, and a proposed layout for the display of data. The final decision on the precision (i.e., number of decimal places) for presentation of descriptive statistics will be made by Galderma after review of draft statistical tables and before database freeze.

Data Listing Conventions

Mock-ups for data listings will include headers, title numbers, titles, column headers, and footers. Data listings will provide all data either collected on the corresponding eCRF page or loaded directly into the database, unless otherwise indicated. If there are too many fields to be fit into a single page, data should be grouped logically and the listings will be generated as Part I, Part II, etc.

In general, data listings should include all subjects with data. However, if only subjects who meet a certain condition are listed (e.g., subjects with SAEs) and no subjects meet the condition, the data listing will so indicate.

Data presented in data listings will be sorted by subject number, unless otherwise requested by Galderma. Within a subject, data will be listed in chronological order. Whenever possible, formatted values will be displayed (i.e., decoded). Where applicable, calendar date and study day of evaluations/events will be provided in the data listings.

14 Preliminary List of Statistical Tables, Listings, and Figures to Be Programmed

14.1 Statistical Tables

Table Number	Table Title	Analysis Population	(U)nique/ (P)roduction
14.1 Demographic Data			
14.1.1	Subject Enrollment and Disposition		U
14.1.2	Demographic and Baseline Characteristics	Safety	U
14.2 Efficacy Data			
14.2.1.1	Reduction in Lesion Counts at Each Scheduled Visit (Observed)	ITT	U
14.2.1.2	Reduction in Lesion Counts at Each Scheduled Visit (LOCF)	ITT	P
14.2.2.1	Percent Reduction in Lesion Counts at Each Scheduled Visit (Observed)	ITT	U
14.2.2.2	Percent Reduction in Lesion Counts at Each Scheduled Visit (LOCF)	ITT	P
14.2.3.1	Summary of IGA Success Rate at Each Visit (Observed)	ITT	U
14.2.3.2	Summary of IGA Success Rate at Each Visit (LOCF)	ITT	P
14.2.4.1.1	Summary of Number and Percent of Subjects Who Are Candidates for Oral Isotretinoin at Each Visit (Observed)	ITT	U
14.2.4.1.2	Summary of Number and Percent of Subjects Who Are Candidates for Oral Isotretinoin at Each Visit (LOCF)	ITT	P
14.2.4.2.1	Summary of Number and Percent of Subjects Who Are Candidates for Oral Isotretinoin at Week 12/ET by Time Since Acne Onset and Gender (Observed)	ITT	U
14.2.4.2.2	Summary of Number and Percent of Subjects Who Are Candidates for Oral Isotretinoin at Week 12/ET by Time Since Acne Onset and Gender (LOCF)	ITT	P
14.2.4.3.1	Summary of Number and Percent of Subjects Who Are Candidates for Oral Isotretinoin at Week 12/ET by Age of Acne Onset and Gender (Observed)	ITT	U

Table Number	Table Title	Analysis Population	(U)nique/ (P)roduction
14.2.4.3.2	Summary of Number and Percent of Subjects Who Are Candidates for Oral Isotretinoin at Week 12/ET by Age of Acne Onset and Gender (LOCF)	ITT	P
14.2.5	Summary of Subject Assessment of Acne Improvement at Week 12/ET	ITT	U
14.2.6	Summary of Subject Satisfaction Questionnaire at Week 12/ET	ITT	U
14.2.7.1	Summary of Number and Percent of Acne-QoL Item Score at Baseline and Week 12/ET	ITT	U
14.2.7.2	Summary of Acne-QoL Item Score and Change from Baseline to Week 12/ET	ITT	U
14.2.7.3	Summary of Acne-QoL Domain Score and Change from Baseline to Week 12/ET	ITT	U
[redacted] CCI			
14.3 Safety Data			
14.3.1 Exposure and Adverse Events			

Table Number	Table Title	Analysis Population	(U)nique/ (P)roduction
14.3.1.1	Exposure to Study Drug	Safety	U
14.3.1.2	Overall Summary of Treatment-Emergent Adverse Events	Safety	U
14.3.1.3	Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	U
14.3.1.4	Treatment-Emergent Adverse Events by Relationship to Study Drug by MedDRA System Organ Class and Preferred Term	Safety	U
14.3.1.5	Treatment-Emergent Adverse Events by Severity by MedDRA System Organ Class and Preferred Term	Safety	U
14.3.2.1	Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	P
14.3.2.2	Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term	Safety	P
Other Safety			
14.3.4.1	Summary of Local Tolerability at Each Visit	Safety	U
14.3.4.2	Shifts from Baseline to Worst On-Treatment Value for Each Local Tolerability Symptom	Safety	U
14.3.4.3	Summary of Local Tolerability and Change from Baseline to Each Visit	Safety	U
14.3.5	Concomitant Medications by WHO Drug Dictionary ATC-3 Code and Preferred Name	Safety	U

14.2 Data Listings

Number	Title	(U)nique/ (P)roduction
16.2.1.1	Study Completion and Discontinuation Information	U
16.2.1.2	Screen Failures	U
16.2.1.3	Study Visits	U
16.2.2 Protocol Deviations		

Number	Title	(U)nique/ (P)roduction
16.2.2.1	Inclusion and Exclusion Criteria Not Met	U
16.2.2.2	Protocol Deviations	U
16.2.4 Demographic Data		
16.2.4.1	Demographics and Baseline Characteristics	U
16.2.4.2	Medical History	U
16.2.4.3	Childbearing Potential	U
16.2.5 Study Drug Administration		
16.2.5.1	Study Drug Accountability - Adapalene 0.3% / Benzoyl Peroxide 2.5% Gel	U
16.2.5.2	Study Drug Accountability - Doxycycline Hyclate	U
16.2.6 Individual Efficacy Response Data		
16.2.6.1	Lesion Counts	U
16.2.6.2	Investigator's Global Assessment	U
16.2.6.3	Oral Isotretinoin Evaluation	U
16.2.6.4	Subject Assessment of Acne Improvement	U
16.2.6.5	Subject Satisfaction Questionnaire	U
16.2.6.6.1	Acne-Specific Quality of Life Questionnaire – Part 1	U
16.2.6.6.2	Acne-Specific Quality of Life Questionnaire – Part 2	P
16.2.6.7.1	Dermatology Life Quality Index (DLQI) – Part 1	U
16.2.6.7.2	Dermatology Life Quality Index (DLQI) – Part 2	P
16.2.6.8.1	Childrens Dermatology Life Quality Index (cDLQI) – Part 1	U
16.2.6.8.2	Childrens Dermatology Life Quality Index (cDLQI) – Part 2	P
16.2.6.9	Photographs	U
16.2.7 Adverse Event Listings		
16.2.7.1	Adverse Events	U
16.2.7.2	Serious Adverse Events	P
16.2.7.3	Adverse Events Leading Discontinuation of Study Drug	P
16.2.8 Listings of Individual Laboratory Measurements		
16.2.8.1	Local Tolerability	U
16.2.8.2	Urine Pregnancy Test	U
16.2.8.3	Prior and Concomitant Medications/Therapies	U
16.2.8.4	Prior and Concomitant Medical/Surgical Procedures	U
16.2.8.5	Comments	U

14.3 Figures

Figure Number	Figure Title	Analysis Population	(U)nique/ (P)roduction
Figure 1	Reasons for Discontinuation from Study (Bar Chart)	ITT	U
Figure 2	Median Percent Reduction from Baseline in Total, Inflammatory, and Non-inflammatory Lesion Counts (LOCF) (Line Chart)	ITT	U
Figure 3	IGA Success Rate at Each Visit (LOCF) (Line Chart)	ITT	U
Figure 4	Oral Isotretinoin Evaluation at Each Visit (Line Chart)	ITT	U
Figure 5	Subject Satisfaction Questionnaire (Bar Chart)	ITT	U
Figure 6	Mean Change from Baseline in Acne-QoL Domain Scores Over Time (Observed) (Line Chart)	ITT	U
Figure 7	Mean Change from Baseline in Local Tolerability Category Scores (Line Chart)	Safety	U