Statistical Analytical Plan

A Multi-Center Clinical Trial to Evaluate the Efficacy of Two Acne Treatments
SPONSOR PROTOCOL GLI.04.SPR.US10354
Stephens' Study Number C16-CD020

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1 Abbreviations and Definitions

AE	Adverse Event
CRF	Case Report Form
eCRF	Electronic Case Report Form
etc.	et cetera
e.g.	for example (Latin; exempla gratia)
FDA	The Food and Drug Administration
GCP	Good Clinical Practice
GLLP	Galderma Laboratories, L.P.
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IPL	Intesnse Pulse Light
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
N or n	Number
OTC	Over-the-Counter
%	Percent
P	Probability (as in significance level)
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analyses Plan
SD	Standard deviation
SOP	Standard Operating Procedure
i.e.	that is (Latin: id est)
USV	Unscheduled Visit

2 Introduction

2.1 Purpose of the Analyses

Acne is an inflammatory disease of the sebaceous gland that occurs during adolescence and persists into adulthood. Non-inflammatory acne lesions form when the opening of the follicle becomes blocked by the presence of dense keratin and sebum. Inflammatory acne lesions develop when the orifice of the follicle becomes completely occluded and bacteria replicate and excrete substances that induce an inflammatory reaction.

Treatment with acne medications has been shown to help dissolve keratin plugs and help prevent the proliferation of bacteria in the sebaceous gland. This results in a reduction in the numbers of non-inflammatory and inflammatory acne lesions.[1,2]

The multicenter, double-blind, randomized, controlled clinical trial is being conducted to evaluate the efficacy of 2 acne treatments for 24 weeks of use in adult men and women 21 to 45 years of age with mild to moderate facial acne, with at least 5 inflammatory lesions, and 10 – 100 non-inflammatory lesions.

3 Study Objectives and Endpoints

3.1 Study Objectives

- To characterize the effect of the acne treatment in lesion count at week 1, week 2, week 6, week 12, and week 24 as compared to baseline and compare between treatments
- To characterize the effect of the acne treatment in Investigator's Global Assessment at week 1, week 2, week 6, week 12, and week 24 as compared to baseline and compare between treatments
- To characterize the effect of the acne treatment in clinical grading of efficacy parameters through digital images at week 6, week 12, and week 24 as compared to baseline and compare between treatments
- To characterize the effect of the acne treatment in subject self-assessment questionnaire responses at week 1, week 2, week 6 week 12, and week 24 as compare between treatments
- To characterize the effect of objective irritation parameters and subjective irritation parameters at week 1, week 2, week 6, week 12, and week 24 as compared to baseline and compare between treatments
- Monitoring of adverse events throughout the course of the study.

3.2 Endpoints

Clinic assessment:

- Lesion count at baseline, week 1, week 2, week 6, week 12, and week 24.
- Investigator's Global Assessment (IGA) at baseline, week 1, week 2, week 6, week 12, and week 24.
- Clinical grading of efficacy parameters through digital images taken at baseline, week 6, week 12, and week 24.
- Clinical grading of tolerance parameters at baseline, week 1, week 2, week 6, week 12, and week 24.
- Digital images at baseline, week 6, week 12, and week 24.

Subject self-assessment:

- Subject self-assessment questionnaires at week 1, week 2, week 6 week 12, and week 24

Safety:

- Number of adverse events

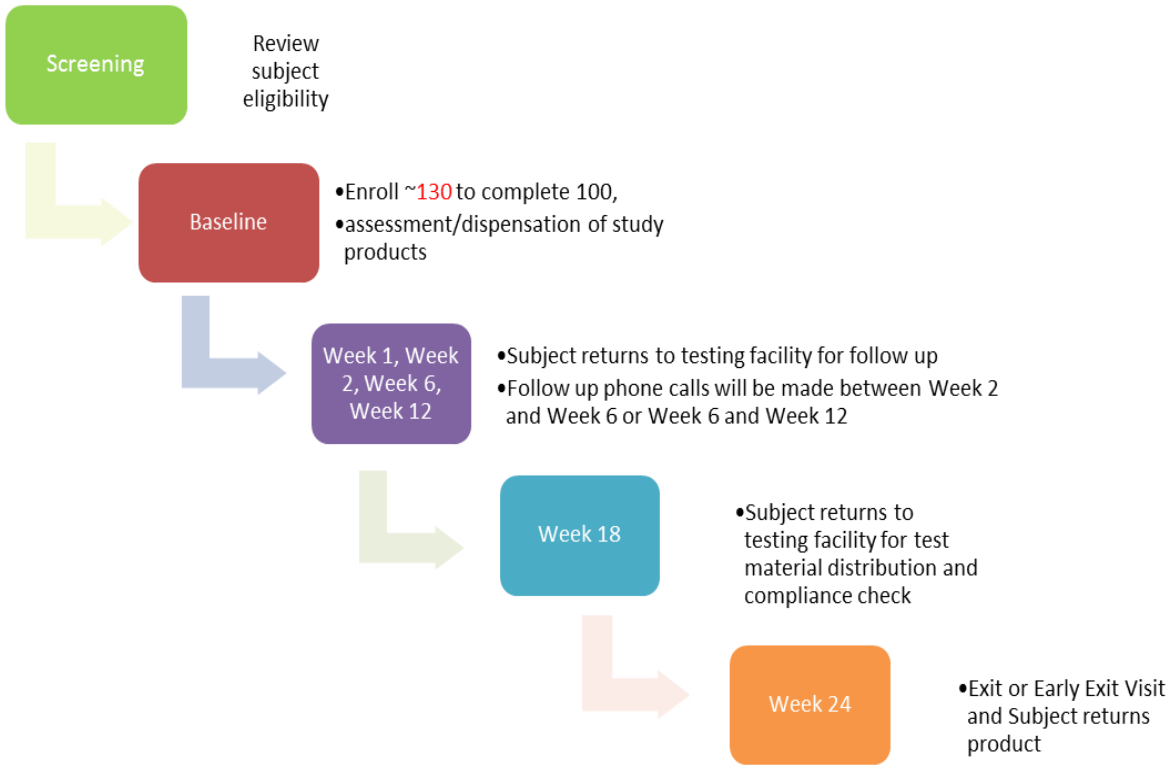
3.3 Derived Variables

None

4 Study Methods

4.1 General Study Design and Plan

- This is a multicenter, double-blind, randomized, controlled clinical trial to be conducted in the United States at 4 testing facilities. The study will examine the effect of 2 acne treatments (Product A when used once daily and Product B when used 1-3 times a day) for 24 weeks in adult men and women 21 to 45 years of age with mild to moderate facial acne, with at least 5 inflammatory lesions, and 10 – 100 non-inflammatory lesions at enrollment. Subjects meeting the inclusion/exclusion criteria are to be enrolled in the study. There will be up to 8 visits during the course of the study: Screening, Baseline, Week 1, Week 2, Week 6, Week 12, Week 18, and Week 24.
- Approximately 130 subjects will be enrolled to complete with 100 subjects (50 per cell). For the purposes of this protocol, enrolled is defined as a subject who has been consented, screened and eligibility has been verified. Each site is to enroll no more than 40 subjects, with at least 100 subjects expected to complete when combined.
- Adverse event assessments will be conducted for all subjects at every visit after Informed Consent is signed.
- Type of control(s): No controls.
- Level and method of blinding: Double-blind.
- Method of treatment assignment: Randomized to use Product A or Product B.
- Sequence and duration of all study periods:



4.2 Inclusion-Exclusion Criteria and General Study Population

Inclusion Criteria

1. Men and women age 21 to 45 years at the time of enrollment.
2. Individuals with mild to moderate acne (score of 2-3 on FDA Investigator's Global Assessment Scale[1]) on the face.
3. Individuals with at least 5 inflammatory lesions.
4. Individuals with 10 – 100 non-inflammatory lesions.
5. Individuals willing to use the test products as instructed for 24 weeks.
6. Fitzpatrick skin type I-VI).
7. Individuals willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol.
8. Individuals willing to provide written informed consent including photo release, Health Insurance Portability and Accountability Act (HIPAA), and are able to read, speak, write, understand English and are willing to share personal information and data, as verified by signing a written authorization at the screening.
9. Willing to withhold all facial treatments during the course of the study including botulinum toxin, injectable fillers, microdermabrasion, IPL, peels, facials, laser treatments and tightening treatments. Waxing and threading is allowed but not facial laser hair removal.
10. Males who are regular shavers and willing to shave on the day of the study visits (prior to clinic visits).
11. Women of child bearing potential who are willing to take a urine pregnancy test prior to study enrollment, at week 24, and when deemed appropriate by the Investigator and/or Sponsor.
12. Individuals of child bearing potential who use an acceptable method of contraception throughout the study. Acceptable methods of birth control include:
    - Oral and other system contraceptives. Individuals must be on a stable use for 3 months prior to study enrollment. Individuals on oral contraceptives must not alter their use, including dose or regimen for the duration of the study
    - Double barrier
    - Bilateral tubal ligation
    - Partner vasectomy
    - Abstinence
13. Individuals willing to follow study requirements and report any changes in health status or medications, adverse event symptoms, or reactions immediately.
14. Subjects must be stable on any medication they are taking for at least 30 days

Exclusion Criteria

1. Individuals diagnosed with allergies to topical acne products.
2. Individuals having a condition and/or disease of the skin that the Investigator deems inappropriate for participation.
3. Women who are nursing, pregnant, or planning to become pregnant during the study.
4. Individuals who have pre-existing or dormant dermatologic conditions on the face (e.g., psoriasis, rosacea, eczema, seborrheic dermatitis, severe excoriations etc.) which in the opinion of the Investigator could interfere with the outcome of the study.
5. Individuals with a history of immunosuppression/immune deficiency disorders (including (HIV infection or AIDS) or currently using immunosuppressive medications (e.g., azathioprine, belimumab, cyclophosphamide, Enbrel, Imuran, Humira, mycophenolate mofetil, methotrexate, prednisone, Remicade, Stelara.).
6. Individuals with an uncontrolled disease such as asthma, diabetes, hypertension, hyperthyroidism, or hypothyroidism. Individuals having multiple health conditions may be excluded from participation even if the conditions are controlled by diet, medication, etc. at the Investigator's discretion.
7. Individuals who are currently participating in another facial usage study or have participated in a clinical trial within 4 weeks prior to inclusion into the study.
8. Individuals with a history of skin cancer on the face within the past 5 years.
9. Individuals with any planned surgeries and/or invasive medical procedures during the course of the study.
10. Individuals who started hormone replacement therapies (HRT) or hormones for birth control less than 3 months prior to study entry or who plan on starting, stopping, or changing doses of HRT or hormones for birth control during the study.
11. Individuals with facial sunburn or excessive tanned facial skin or that are not willing to avoid daily sun

exposure on the face and the use of tanning beds or sunless tanning products for the duration of the study.
12. Individuals with severe acne, acne conglobata, multiple nodules or cysts (more than 2).
13. Individuals currently taking a natural or prescription testosterone blocker (e.g. saw palmetto, blask cohosh, chaste tree, chasteberry, spironolactone, drospirenone, progestins).
14. Individuals currently on a testosterone booster or prescription testosterone (e.g. DHEA, tribulus, testosterone cypionate, testosterone enanthate, Sustanon, testosterone propionate, testosterone phenylpropriate, Omnadren etc.).
15. Individuals that are currently taking or have taken within the last 30 days oral or topical prescription medications for acne such as Doxycycline, Minocycline, Clindamycin, Bactrim, Tetracycline, Erythromycin, Vibramycin and topical tretinoin.(Retin A Renova, Adapalene, Tazarotene), Azelaic acid, benzoyl peroxide, Dapsone, Sodium sulfacetamide, Differin, Epiduo.
16. Individuals that have used oral isotretinoin (Accutane) within the past 6-months.
17. Individuals routinely using (3x a week or more) topical OTC acne product (e.g. benzoyl peroxide, salicylic acid, alpha hydroxyl, beta hydroxyl and/or poly-hydroxy products or medicated cleansers, wipes, masks, scrubs, gels and creams) within 14 days of the study entry.
18. Individuals using or who have used any systemic medication considered to affect the course of acne, specifically, but not exclusively antibiotics or steroids within the last 30 days prior to entry into the study.
19. Individuals with excessive facial hair, including beard, mustache or goatee, or scars, which could interfere with evaluations by Investigator or designee.

4.3 Study Variables

4.3.1 Lesion Count (Clinic Day Assessments: Screening/Baseline, Week 1, Week 2, Week 6, Week 12, Week 24)

A trained grader will count and record the number of open comedones, closed comedones papules, and pustules on each subject's face. Note that papules and pustules are classified as inflammatory acne lesions while open and closed comedones are classified as non-inflammatory lesions.

Acne lesion counts will be assessed globally on the face for each of the following facial locations/quadrants: forehead, left cheek, chin (including the area above the upper lip), and right cheek. Lesions on the nose, under the jaw line or along the hairline (including eye brows) will not be included in the counts[3].

4.3.2 Investigator's Global Assessment (IGA) (Clinic Day Assessments: Screening/Baseline, Week 1, Week 2, Week 6, Week 12, and Week 24)

A trained grader will evaluate each subject's global face for Investigator's Global Improvement Assessment.

FDA Investigator's Global Assessment of Acne Severity scale

0	Clear	No inflammatory or non-inflammatory lesions
1	Almost Clear	Rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild	Greater than Grade 1, some non-inflammatory lesions with no more than a few inflammatory lesion (papules/pustules only, no nodular lesions)
3	Moderate	Greater than Grade 2, up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4	Severe	Greater than Grade 3, up to many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions

4.3.3 Clinical Grading of Efficacy Parameters though Digital Images (Clinic Day Assessments: Baseline, Week 6, Week 12, and Week 24)

Stephen's trained grader will evaluate each digital images for clinical grading of efficacy parameters. The efficacy parameters will be assessed globally on each subject's face using a modified Griffiths' 10-point scale according to the following numerical definitions (half-point scores may be used as necessary to more accurately describe the skin condition):
0 = none (best possible condition)
1 to 3 = mild
4 to 6 = moderate
7 to 9 = severe (worst possible condition)
The following parameters will be evaluated using the indicated scale anchors:

Parameter	0 =	9 =
Skin texture	Smooth, even looking skin texture	Rough, uneven looking skin texture
Skin tone evenness	Even skin tone	Severely uneven skin tone
Clarity	Translucent skin appearance	Dull/flat matte skin appearance
Overall skin complexion	Excellent	Poor

4.3.4 Tolerability Evaluation (Clinic Day Assessments: Screening/Baseline, Week 1, Week 2, Week 6, Week 12, Week 24)

Tolerability evaluations will be performed at screening, baseline, and weeks 1, 2, 6, 12, and 24. Local cutaneous tolerability will be evaluated by assessing the signs and symptoms of erythema, dryness, and scaling, and by subject reporting of the degree of stinging/burning on the global face (treatment area).
For subject assessments of subjective irritation, subjects will report the degree of any parameters that they typically experience when using a product similar to the test material(s) at the baseline visit. At post-baseline time points, subjects will report the degree of any of these symptoms they have experienced since the previous time point.
The following static (without reference to any prior visits) scales and definitions will be used for tolerability evaluations (with half-point scores used as necessary to better describe the clinical condition):

Objective Irritation Parameters

Erythema

0 = None	No erythema of the treatment area
1 = Mild	Slight, but definite redness of the treatment area
2 = Moderate	Definite redness of the treatment area
3 = Severe	Marked redness of the treatment area

Dryness

0 = None	No dryness of the treatment area
1 = Mild	Slight, but definite dryness of the treatment area
2 = Moderate	Definite dryness of the treatment area
3 = Severe	Marked dryness of the treatment area

Scaling

0 = None	No scaling of the treatment area
1 = Mild	Barely perceptible, fine scales in limited areas of the treatment area
2 = Moderate	Fine scaling generalized to all areas of the treatment area
3 = Severe	Scaling and peeling of skin over all areas of the treatment area

Subjective Irritation Parameters

Burning/stinging

0 = None	No burning/stinging of the treatment area
1 = Mild	Slight burning/stinging sensation of the treatment area; not really bothersome
2 = Moderate	Definite warm, burning/stinging of the treatment area that is somewhat bothersome
3 = Severe	Hot burning/marked stinging sensation of the treatment area that causes definite discomfort and may interrupt daily activities and/or sleep

4.3.5 Digital Images (Clinic Day Assessments: Baseline, Week 6, Week 12, and Week 24)

Prior to photography procedures, clinic personnel will ensure that subjects have a clean face with no makeup as described in the study procedures. Subjects will remove any jewelry from the area(s) to be photographed and equilibrate for at least 15 minutes to ambient conditions (68-75ºF and 35-65% humidity) within the clinic before any photographs are taken.

VISIA Imaging:

Subjects will be provided with a black or gray matte headband to keep hair away from the face and instructed on proper headband placement. Subjects will be provided with a black matte shirt or a black or gray matte cloth will be draped over the subjects' clothing. Subjects will be instructed to adopt neutral, non-smiling expressions with their eyes gently closed. Subjects will be carefully positioned for each photograph, for the center, right, and left side views.

Full-face digital images will be taken of each subject (right side, left side, and center views) using the VISIA CR photo-station (Canfield Imaging Systems, Fairfield, New Jersey) with a Canon Mark II 5D or 6D digital SLR camera (Canon Incorporated, Tokyo, Japan) under the following lighting conditions:

Standard lighting 1
Standard lighting 2
Cross-polarized
Parallel polarized
UV fluorescence

Visible Light Imaging (Beauty shot)

For subjects completing at sites 1 and 2 (Stephens' Texas and Colorado locations), digital images will be taken of each subject's face using visible light. Full-face images will be taken of each subject's center view. Subjects will not be wearing any headband or using any headrest/chinrest. Subjects will be instructed to adopt neutral, non-smiling expressions with their eyes open.

4.3.6 Self-Assessment Questionnaires (Clinic Day Assessment: Baseline, Week 1, Week 2, Week 6, Week 12, and Week 24)

Subjects will be asked to complete a self-assessment questionnaire. This questionnaire has a 5-point Likert Response Scale (1=Strongly Agree; 5=Strongly Disagree). Responses for each item will be transformed into percent agreement (percentage of subjects with a score of 1 or 2) and presented descriptively. The individual items will be asked at the indicated time points:

Questions	Visit 2: Week 1	Visit 3: Week 2	Visit 4: Week 6	Visit 5: Week 12	Visit 7: Week 24
I experienced noticeable improvement in my skin tone				X	X
I experienced noticeable improvement in my skin texture				X	X
I experienced noticeable improvement in my skin radiance				X	X
My skin has a more youthful appearance				X	X
My skin is clearer skin using this treatment		X	X	X	X
I feel my skin is now clear			X	X	X
This treatment works faster than my previous acne treatment.	X	X			
This treatment is strong enough to give me clear, acne free skin.				X	X
The treatment helped to reduce redness and inflammation caused by my acne.			X	X	X
I feel that this treatment deep cleans and unblocks my pores.	X	X	X		

This treatment visually minimized my pore size.			X	X	X
I noticed an improvement in my acne. Strongly agree to Strongly disagree	X	X			X
This treatment reduces my acne without leaving behind dry, flakey skin.			X	X	X
I have noticed I had fewer breakouts than my previous treatments.	X	X	X	X	X
My skin looks better than before			X	X	X
This treatment breaks my cycle of acne and keeps my skin clear				X	X
I saw improvement in the overall health of my skin since starting the regimen	X		X	X	X
My skin looks noticeably smoother and healthier			X	X	
The areas of my skin where I used to have acne is now clear and radiant after daily treatment.		X	X	X	X
I feel better about my skin since I've started the treatment regimen			X	X	X
I feel more confident since I've started the treatment			X	X	X
Has your quality of life improved now that you have started using this product?				X	X
I would continue using this treatment beyond 24 weeks as a regular part of my skincare routine.					X
What is your overall satisfaction with the regimen?			X	X	X
I have noticed a positive difference in the appearance of my skin with this regimen.			X	X	X
This once a day regimen is easy to use every day.	X		X		
I liked the feel of this product.	X				
I would recommend this product to others.				X	X
My acne is as clear as if I went to a doctor or received a prescription.				X	X
I don't feel the need for a prescription after using this product.				X	X
Total:	7	6	16	24	25

5 Sample Size

Approximately 130 subjects will be enrolled to complete with 100 subjects (50 per cell). For the purposes of this protocol, enrolled is defined as a subject who has been consented, screened and eligibility has been verified. Each site is to enroll no more than 40 subjects, with at least 100 subjects expected to complete when combined. Sample size is determined according to Sponsor's recommendation.

6 General Considerations

6.1 Timing of Analyses

The final analysis will be performed after all subjects exit from the study.

6.2 Analysis Populations

All statistical analyses will be performed based on the following subject populations. Data from the 4 sites will be pool together prior to the statistical analysis.

6.2.1 Intent-to-Treat (ITT) Population

The ITT population is defined as all subjects who are randomized and have at least one post-treatment administration evaluation. This is the primary population for efficacy analyses. All primary efficacy variables and secondary efficacy variables will be analyzed based on the ITT population. LOCF (Last Observation Carried Forward) will be used to impute missing efficacy data for this population.

6.2.2 Safety Population

The safety population is defined as all subjects who are enrolled and receive at least one dose of study product. In practice, only the subjects who return their study product unopened will be excluded from the safety population. Safety variables will be analyzed based on the safety population.

6.3 Missing Data

If there are missing post-baseline data of primary and secondary variables for the ITT population, these data will be imputed using the LOCF method.
For the safety population, all evaluable data obtained will be used. No imputation will be carried forward for the missing data. In addition, missing last used date will be imputed using the last visit date and the missing first used date will be imputed using the baseline date.

6.4 Interim Analyses and Data Monitoring

Interim analyses will be performed after Week 1, 2, 6 and 12 visit. No other interim analyses will be conducted.

The conduct of the study will be closely monitored by representatives of GLLP following GCP, ICH guidelines, applicable SOPs, regulatory guidelines and all local regulations. The clinical investigation will be monitored to ensure that: the rights and well-being of the subjects are protected; the reported data are accurate, complete and verifiable from applicable source documents; and the study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements. The investigator will allow the GLLP representatives to have access to all study records, CRF, corresponding subject medical records, and any other documents considered source documentation. The investigator also agrees to assist the representatives, if required, which can include AE reporting.

7 Summary of Study Data

The subject disposition, demographics, baseline characteristics, compliance (number of missed applications, total number of applications, etc.), visit dates including informed consent date, inclusion/exclusion criteria, previous therapies and concomitant therapies by treatment will be listed or summarized. All primary and safety variables listed will be summarized at each visit. The categorical variables will be summarized by frequency and percentage for each response category (N, %). The continuous variables will be summarized using means, medians, minimum, maximum, and standard deviations (SD) for each visit.
Additional summary tables will be provided for AEs that are considered serious (SAEs), related to the study product, and AEs leading to discontinuation. All AE summary tables are based on the number of subjects in safety population who have experienced AE(s). For a given AE, a subject will be counted once, even if he or she has experienced multiple episodes for that particular AE.

7.1 Subject Disposition

The summary will be produced in accordance with section 12.

7.2 Protocol Deviations

The summary will be produced in accordance with section 12.

7.3 Demographic and Baseline Variables

The following demographic parameters will be captured at the screening visit:

- Age
- Gender
- Ethnicity and Race (subject self-identified)
- Fitzpatrick Skin Type Classification

The summary will be produced in accordance with section 12.

7.4 Medical History and Current Medical Condition

A listing of medical history and current medical condition will be provided.

7.5 Prior and Concomitant Medications/Therapies

A listing of prior and concomitant medications/therapies will be provided.

7.6 Treatment Compliance

Compliance will be assessed from subjects' daily diary where test material applications will be recorded. Subjects will be considered compliant with the treatment product if they use at least 80% of the expected applications for each of the test product during participation in the study. Subjects will be considered non-compliant if usage is over 120%. The percent dosing compliant subjects received (= number of product use recorded in diary / number of excepted application*100%) of each subject will be reported in a data listing. The percent dosing compliant subjects received will be summarized. The number and percent of subjects who take 80-120% of the expected applications will also be reported.

8 Efficacy Analyses

8.1 Lesion Count, Investigator's Global Assessment (IGA), Clinical Grading of tolerance parameters and Clinical Grading of Efficacy Parameters through Digital Images

A descriptive statistical summary will be provided. The descriptive statistical summary includes the number of observations (N), mean, median, standard deviation (SD), minimum (MIN) and maximum (MAX) of scores/values at all applicable time points. Mean of the change from baseline (defined as post-baseline value minus baseline value) will be estimated at post-baseline time points. The null hypothesis, that the mean change from baseline is zero, will be tested. Wilcoxon signed-rank test will be employed.
The following will be calculated and reported for each evaluation parameter at the applicable post-baseline time point(s):

$$\text{Percent mean change from baseline} = \frac{(\text{visit mean score} - \text{baseline mean score}) \times 100}{\text{baseline mean score}}$$

$$\text{Percent of subjects improved/worsened} = \frac{(\text{number of subjects improved/worsened from baseline}) \times 100}{\text{total number of subjects}}$$

For applicable parameters, comparisons between the treatment cells will be made in terms of changes from baseline. The null hypothesis, that the mean change from baseline is equal between the 2 treatment cells at post-baseline time points, will be tested using a Wilcoxon rank sum test.

Each of the following lesions will be analyzed separately for forehead, left cheek, chin, right cheek, and the total of 4 areas as global face:

- Inflammatory acne lesions (sum of papules and pustules)
- Non-inflammatory acne lesions (sum of open comedones and closed comedones)
- Total lesion counts (sum of inflammatory and non-inflammatory acne lesions counts

8.2 Subject Satisfaction Questionnaire

For Subject Satisfaction Questionnaire data, a tabulation including frequency and percentage of all response options will be reported for each question. In addition, frequency and percentage of agree (combining "Strongly Agree" and "Agree"), neutral ("Neither Agree nor Disagree") and disagree (combining "Strongly Disagree" and "Disagree") will also be reported for each question. A binomial (sign) test will be performed to test if the proportion of the combined agree responses is equal to the combined disagree responses for each applicable question. For applicable questions, responses will also be compared between treatments by Fisher's exact test. The test null hypothesis is that the proportion of the combined agree responses is equal between treatment cells. A more appropriate analysis may be performed based on the questionnaire design, which will be recorded in a note to file and in the study report.

9 Safety Analyses

9.1 Adverse Events, Serious Adverse Events and other Significant Adverse Events

Adverse events will be summarized. A listing of adverse events will be provided.
Additional summary tables will be provided for AEs that are considered serious (SAEs), related to the study product, and AEs leading to discontinuation. All AE summary tables are based on the number of subjects who have experienced AE(s). For a given AE, a subject will be counted once, even if he or she has experienced multiple episodes for that particular AE.

9.2 Pregnancies

Pregnancy test will be performed at screening and week 24/early exit. These data will not be statistically analysed.

10 Reporting Conventions

- All statistics will be reported to one decimal place unless specified.
- All statistical tests will be 2-sided at significance level alpha=0.05. P-values will be reported to 3 decimal places (0.000). P-values less than 0.001 will be displayed as <0.001.

11 Technical Details

SAS software version 9.30 or later (*(SAS Statistical Institute).*) will be used to statistically analyze the data and all output will be in Excel formats.

12 Listing of Tables, Listings and Figures

The data will not be presented in Figures for this study.

The following listings will be made and submitted along with the final report:

- Subject Demographics and Disposition
- Subject Compliance (individual responses to product usage compliance query at applicable visits, subject's visit dates, Informed Consent and Inclusion/Exclusion tables)
- Concomitant Medications/ Therapies
- Subject's Medical History (including medical and surgical procedures)
- Adverse Events
- All efficacy and tolerability endpoints: lesion count, Investigator's global assessment (IGA), clinical grading of tolerance parameters, clinical grading of efficacy parameters through digital images, and subject satisfaction questionnaire
- Protocol deviations

The listings will contain a minimum of the following:

- Title
- Footnotes (if any)
- Population
- Endpoint(s)
- Time Points
- Summary statistics

The following is a partially complete example of listing of tables:

Table Title	Population	Endpoint	Time Points	Summary Statistics	Formal Analysis	Foot Notes
Subject Demographics	All enrolled	Age, Gender, Ethnicity and Race, Fitzpatrick Skin Type	Screening	N, Mean, SD, Median, Min-Max, Percent	NA	
Subject Disposition	All enrolled	Disposition	Screening, Baseline-Week 24	NA	NA	
Individual responses to product usage compliance query	All enrolled	N (%) of dosing compliant subjects	Week 1 - Week 24	N, Percent	NA	
Subject's visit dates	All enrolled	All visits	Screening, Baseline – Week 24	NA	NA	
Informed Consent	All enrolled	Date of signature	Screening	NA	NA	
Inclusion/Exclusion	All enrolled	Inclusion Criteria and Exclusion Criteria	Screening	NA	NA	
Concomitant Medications/ Therapies	All enrolled	Medication, Dose and units, Frequency, Route, Indication, start and stop date, Ongoing or not, relation to AE	Screening, Baseline – Week 24	NA	NA	
Subject's Medical History (including medical and surgical procedures)	All enrolled	Condition/surgery/ procedure and start/stop dates	Screening	NA	NA	
Urine Pregnancy test	All enrolled	Date, positive/negative	Screening and week 24	NA	NA	
Lesion count	ITT	Number of open comedones, closed comedones, papules, and pustules on forehead, left cheek, chin and right cheek on each subject's face	Screening, Baseline – Week 24 (except week 18)	Summary of N, Mean, SD, Median, Min-Max, change from baseline statistics, treatment comparisons	NA	
Investigator's Global Assessment	ITT	Investigator's global assessment of acne severity	Screening, Baseline – Week 24 (except week 18)	Summary of N, Mean, SD, Median, Min-Max, a change from baseline statistics, treatment comparisons	NA	
Clinical Grading of Tolerance Parameters	ITT	Erythema, dryness, scaling, burning/stinging	Screening, Baseline – Week 24 (except week 18)	Summary of N, Mean, SD, Median, Min-Max, change from baseline statistics, treatment	NA	

Table Title	Population	Endpoint	Time Points	Summary Statistics	Formal Analysis	Foot Notes
				comparisons		
Clinical Grading of Efficacy Parameters through Digital Images	ITT	Lines/wrinkles (if present), skin texture, skin tone evenness, clarity, and overall skin complexion	Baseline, Week 6, Week 12, and Week 24	Summary of N, Mean, SD, Median, Min-Max, change from baseline statistics, treatment comparisons	NA	
Digital Imaging	ITT	N/A	Baseline, Week 6, Week 12, and Week 24	NA	Stephens will not perform image analysis	
Self-Assessment Questionnaire	ITT	Self-Assessment Questionnaire	Week1 – Week 24	N, Percent, sign test, treatment comparisons	NA	
Adverse Events	Safety	Description of event, start and stop date, Frequency, Severity, Relationship to test product, Action taken, Treatment and Final outcome	Baseline – Week 24	NA	NA	

13 References

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4. Griffiths CE, Wang TS, Hamilton TA, Voorhees JJ, Ellis CN. A photonumeric scale for the assessment of cutaneous photodamage. Arch Dermatol. 1992 Mar;128(3):347-351.