CLINICAL STUDY PROTOCOL

IDP-126

Protocol V01-126A-202

A Phase 2, Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Clinical Study to Compare the Safety and Efficacy of IDP-126 Gel to Epiduo® Forte Gel (0.3% adapalene/2.5% BPO), in the Treatment of Acne Vulgaris

Development Phase:	2
Study Design:	Multicenter, randomized, double-blind, vehicle-controlled efficacy and safety study
Date:	Version 2.0, 2 March 2021 (Amendment 1) Version 1.0, 30 October 2020 (Original)
Sponsor:	Bausch Health Americas, Inc. 1330 Redwood Way Petaluma, CA 94954
For EU:	EudraCT No.: 2021-000100-37

BAUSCH Health

Protocol Review and Approvals

A Phase 2, Multicenter, Randomized, Double-Blind, Vehicle-Controlled Clinical Study to Compare the Safety and Efficacy of TDP-126 Gel to Epiduo® Forte Gel (0.3% adapalene/2.5% BPO) in the Treatment of Acne Vulgaris

[redacted]

Protocol Review and Approvals

A Phase 2, Multicenter, Randomized, Double-Blind, Vehicle-Controlled Clinical Study to Compare the Safety and Efficacy of IDP-126 Gel to Epiduo® Forte Gel (0.3% adapalene/2.5% BPO) in the Treatment of Acne Vulgaris

Personnel Responsible for Conducting the Study

A Phase 2, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, Clinical Study to Compare the Safety and Efficacy of IDP-126 Gel to Epiduo® Forte Gel (0.3% adapalene/2.5% BPO), in the Treatment of Acne Vulgaris

Contract Research Organization / Medical Monitor

Principal Investigator Protocol Agreement Page

I agree:

- To assume responsibility for the proper conduct of this clinical study at this study center and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol, written informed consent, consent form updates, subject-recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study.
- To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies).
- That I am thoroughly familiar with the appropriate use of the study drugs(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current Investigator Brochure or equivalent document and approved product label (if applicable).
- To provide sufficient time, and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, study drug(s), and their clinical study-related duties and functions.

_____

Principal Investigator (print name)

_____ _____

Principal Investigator (signature) Date

2 Synopsis

Name of Sponsor/Company: Bausch Health Americas, Inc.
Name of Investigational Product: IDP-126 Gel
Name of Active Ingredients: Fixed combination of clindamycin phosphate 1.2%, benzoyl peroxide (BPO) 3.1%, and adapalene 0.15%
Title of Study: A Phase 2, Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Clinical Study to Compare the Safety and Efficacy of IDP-126 Gel to Epiduo® Forte Gel (0.3% adapalene/2.5% BPO), in the Treatment of Acne Vulgaris
Number of Clinical Centers: Multicenter, approximately 40 study centers in North America and Europe
Objective: The primary objective of this study is to establish a clinical bridge for IDP-126 Gel (clindamycin phosphate 1.2%, benzoyl peroxide [BPO] 3.1%, and adapalene 0.15%) to the comparator drug Epiduo® Forte Gel (0.3% adapalene and 2.5% BPO) in subjects with moderate to severe acne vulgaris. The safety and efficacy of once daily application of IDP-126 Gel will be compared to Epiduo® Forte and IDP-126 Vehicle Gel.
Methodology: This is a multicenter, randomized, double-blind, vehicle-controlled, 12-week study designed to assess the safety, tolerability, and efficacy of IDP-126 Gel in comparison with Epiduo® Forte gel and IDP-126 Vehicle Gel at Weeks 2, 4, 8, and 12. To be eligible for the study, subjects must be at least 12 years of age and have a clinical diagnosis of moderate to severe acne (defined as an Evaluator's Global Severity Score [EGSS] of 3 or 4), presenting with 30-100 inflammatory facial lesions (papules, pustules, and nodules), 35-150 non-inflammatory facial lesions (open and closed comedones), and ≤ 2 facial nodules. All subjects will receive once daily, topically applied treatment to the face for 12 weeks. Subject visits include Screening, Baseline, Week 2, Week 4, Week 8, and Week 12, at which safety and efficacy assessments will be conducted (Screening and Baseline may occur on the same day if no washout is required). One pump of study drug will be dispensed to the subjects at the Baseline, Week 4, and Week 8 study visits. Subjects will be evaluated for drug usage compliance at each post baseline study visit (Weeks 2, 4, 8, and 12). Subjects will apply their treatments at home, once daily (in the evening), as instructed by the study coordinator or designee at each study center. The investigator will assess the subject's face at each study visit. Though not a requirement for study inclusion, the subject may be assessed for truncal acne (neck, upper chest, upper back and shoulders). If the subject has truncal acne and would like to apply study drug to these area(s) a separate evaluation will be performed to assess truncal acne using a Truncal Severity Score (TSS). TSS will be conducted at Baseline, Week 2, Week 4, Week 8, and Week 12. Subject participation in treatment of truncal acne is not a requirement. Information on reported and observed AEs will be obtained at each visit. An abbreviated physical examination and vital sign measurements will be performed at Baseline and Week 12 (end of study) for all subjects. Blood samples will be collected from subjects at Baseline and Week 12, for CBC/Diff and serum chemistry. For all female subjects of childbearing potential (FOCBP), urine pregnancy testing will be performed at Screening, Baseline (prior to randomization), and at Weeks 2, 4, 8, and 12. Additionally, serum pregnancy testing will be performed at Baseline and Week 12. In addition, at selected study centers, standardized photography of the face will be performed at Baseline, and Weeks 4, 8 and 12.
Number of subjects planned: Approximately 660 subjects will be randomized in a 2:2:1:1 ratio to the following treatment groups: • 220 Subjects to IDP-126 Gel (clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15%) • 220 Subjects to Epiduo® Forte Gel (adapalene 0.3%/BPO 2.5%) • 110 Subjects to IDP-126 Vehicle Gel (stored at 2-8°C)

- 110 Subjects to IDP-126 Vehicle Gel (stored at controlled room temperature (CRT))

Inclusion criteria:

1. Male or female at least 12 years of age and older.
2. Written and verbal informed consent must be obtained. Subjects less than age of consent must sign an assent for the study and a parent or a legal guardian must sign the informed consent (if subject reaches age of consent during the study they should be re-consented at the next study visit).
3. Subject must have an EGSS of 3 (moderate) or 4 (severe) at the baseline visit.
4. Subjects with a facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 30, but no more than 100.
5. Subjects with a facial acne non-inflammatory lesion (open and closed comedones) count no less than 35, but no more than 150.
6. Subjects with 2 or fewer facial nodules.
7. FOCBP and females who are premenses must be willing to practice effective contraception for the duration of the study. (Effective contraception is defined as stabilized on oral [either combined estrogen and progestogen containing of progestogen only] contraceptive for at least 3 months, intrauterine device/system, condom with spermicide, diaphragm with spermicide, implant, NuvaRing®, injection, transdermal patch, bilateral occlusion, vasectomized partner, or abstinence.) Females on birth control pills must have taken the same type pill for at least 3 months prior to entering the study and must not change type during the study. Those who have used birth control pills in the past must have discontinued usage at least 3 months prior to the start of the study. Women who use birth control for acne control only should be excluded.
8. Premenses females and FOCBP must have a negative urine pregnancy test at Screening Visit, and a negative urine pregnancy test at Baseline Visit.
9. Subjects must be willing to comply with study instructions and return to the clinic for required visits. Subjects under the age of consent must be accompanied by the parent or legal guardian at the time of assent/consent signing;
10. If a cleanser, moisturizer or sunscreen is needed during the study, subjects must be willing to use only allowed cleansers, moisturizers, sunscreens, or moisturizer/sunscreen combination products (see Appendix 17.2). Subjects must agree to use non-comedogenic products (including makeup and shaving products).

Exclusion Criteria:

1. Use of an investigational drug or device within 30 days of enrollment or participation in a research study concurrent with this study.
2. Any dermatological conditions on the face that could interfere with clinical evaluations such as acne conglobata, acne fulminans, secondary acne, perioral dermatitis, clinically significant rosacea, gram-negative folliculitis, dermatitis, eczema.
3. Any underlying disease(s) or some other dermatological condition of the face that requires the use of interfering topical or systemic therapy or makes evaluations and lesion count inconclusive.
4. Subjects with a facial beard or mustache that could interfere with the study assessments.
5. Subjects with more than 2 facial nodules.
6. Evidence or history of cosmetic-related acne.
7. Subject has a history of experiencing significant burning or stinging when applying any facial treatment (eg, makeup, soap, masks, washes, sunscreens, etc) to their face.
8. Female subjects who are pregnant, nursing mothers, planning a pregnancy during the course of the study, or become pregnant during the study.
9. Use of estrogens (eg, Depogen, Depo-Testadiol, Gynogen, Valergen, etc) for less than 12 weeks immediately preceding study entry; subjects treated with estrogens 12 or more consecutive weeks immediately prior to study entry need not be excluded unless the subject expects to change dose, drug or discontinue estrogen use during the study.
10. If female, subject has a history of hirsutism, polycystic ovarian disease or clinically significant menstrual irregularities.

11. History of regional enteritis, ulcerative colitis, inflammatory bowel disease, pseudomembranous colitis, chronic or recurrent diarrhea, or antibiotic-associated colitis.
12. Treatment of any type of cancer within the last 6 months, with the exception of complete surgical excision of skin cancer outside the treatment area.
13. Subject uses medications and/or vitamins during the study which are reported to exacerbate acne (azathioprine, haloperidol, Vitamin D, Vitamin B12, halogens such as iodides or bromides, lithium, systemic or topical mid-to super-high potency corticosteroids on the treatment area, phenytoin and phenobarbital). Multivitamins, including Vitamin A, at recommended daily doses and Vitamin D at stable doses, are acceptable.
14. History of hypersensitivity or allergic reactions to any of the study preparations as described in the Investigator's Brochure, including known sensitivities to any dosage form of clindamycin phosphate, BPO, or adapalene.
15. Concomitant use of potentially irritating over-the-counter products that contain ingredients such as BPO, alpha-hydroxy acid, salicylic acid, retinol or glycolic acids.
16. Subjects who have not undergone the specified washout period(s) for the following topical preparations/physical treatments used on the face or subjects who require the concurrent use of any of the following in the treatment area:

Topical astringents and abrasives on the face	1 week
Non-allowed moisturizers or sunscreens on the face	1 week
Antibiotics on the face	2 weeks
Other topical anti-acne drugs on the face	2 weeks
Soaps containing antimicrobials on the face	2 weeks
Anti-inflammatory agents and corticosteroids on the face	4 weeks
Retinoids, including retinol on the face	4 weeks
Chemical peel/microdermabrasion on the face	4 weeks
Light (eg. LED, PDT) therapy on the face	4 weeks
Acne surgery	4 weeks
Laser therapy on the face	4 weeks

17. Subjects who have not undergone the specified washout period(s) for the following systemic medications or subjects who require the concurrent use of any of the following systemic medications:

Corticosteroids (including intramuscular injections) (inhaled corticosteroids allowed)	4 weeks
Antibiotics	4 weeks
Other systemic acne treatments	4 weeks
Systemic retinoids	6 months

18. Subjects who intend to use a tanning booth or sunbathe during the study.
19. Subjects who are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
20. Subjects with any underlying disease that the investigator deems uncontrolled, and who pose a concern for the subject's safety while participating in the study.

Investigational product, dosage and mode of administration:

Investigational Product: IDP-126 Gel (clindamycin phosphate 1.2%, BPO 3.1%, and adapalene 0.15%), applied topically to the face once daily for 12 weeks.

Duration of treatment:

12 weeks for all subjects.

Reference therapy, dosage and mode of administration:

- Epiduo® Forte Gel (adapalene 0.3%/ 2.5% BPO) applied once daily for 12 weeks.
- IDP-126 Vehicle Gel (stored at 2-8°C) applied once daily for 12 weeks.
- IDP-126 Vehicle Gel (stored at controlled room temperature) applied once daily for 12 weeks.

Criteria for evaluation:

Co-Primary efficacy:

IDP-126 Gel will be compared to Epiduo® Forte Gel and IDP-126 Vehicle Gel.

Co-primary endpoints are:

(1) Absolute change from Baseline to Week 12 in inflammatory lesion counts.
(2) Absolute change from Baseline to Week 12 in non-inflammatory lesion counts.
(3) Percentage of subjects who achieve at least a two-grade reduction from baseline and are "Clear" or "Almost Clear" at Week 12 in the Evaluator's Global Severity Score.

Secondary efficacy:

The secondary endpoints to be summarized using descriptive statistics are:

(1) Absolute change in inflammatory and non-inflammatory lesion counts from baseline at Weeks 2, 4 and 8
(2) Percent of subjects who achieve at least a 2-grade reduction from baseline and are "clear" or "almost clear" at Week 2, 4 and 8 on EGSS
(3) Mean percent change in inflammatory and non-inflammatory lesion counts from baseline at Weeks 2, 4, 8 and 12.

Efficacy Measurements:

Lesion Counts

At each visit, the evaluator will count the total number of inflammatory lesions (papules, pustules, and nodules) on the subject's face. Nodules will be counted separately but will be included in the total inflammatory lesion count. At baseline, eligible subjects may have no more than 2 nodules. Nodules will be included in the statistical analysis of inflammatory lesion counts. All inflammatory lesions will be counted at the same time rather than counting papules and pustules separately. The evaluator will also count the total number of non-inflammatory lesions (open and closed comedones). The same blinded evaluator should perform the lesion counts and EGSS evaluations at all visits from baseline to week 12 for the same subject, whenever possible. Note: truncal lesions counts will <u>not</u> be performed for subjects participating in truncal acne treatment.

Inflammatory lesions are defined as follows:

Papule: An erythematous, raised, palpable lesion less than 5 mm in diameter
Pustule: An erythematous, raised, likely palpable lesion containing white exudate or pus less than 5 mm in diameter
Nodule: A deep-seated, erythematous, firm lesion greater than 5 mm in diameter

Non-inflammatory lesions are defined as follows:

Open comedone (blackhead): A widely dilated sebaceous follicle plugged with darkly pigmented sebum
Closed comedone (whitehead): A small, closed sebaceous follicle distended with sebum, with a white appearance

Evaluator's Global Severity Score (EGSS)

At each visit, the severity will be determined based on evaluator-blinded evaluations of the signs and symptoms of acne vulgaris. Every effort should be made to have the same evaluator assess the same subject at each visit. If this is not possible, the same evaluator should assess the subject at both the Baseline and Week 12 visits. Evaluations of the face will be scored on a scale of 0-4, with 0 being clear and 4 being severe. Please see the table below for complete definitions. The EGSS should always be completed prior to the lesion counts.

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be 1 nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to 2 nodulocystic lesions

Truncal Severity Score (TSS)

For any subjects participating in the treatment of truncal acne (optional), Investigators will use the TSS scale below to grade truncal acne at each visit (starting at Baseline), recording the score as a separate score from the facial EGSS acne score on a separate TSS form.

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be 1 nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to 2 nodulocystic lesions

Safety Measurements:

Safety evaluations will include the following:

- The percent of subjects who experience a cutaneous reaction (erythema, scaling, hypo/hyper-pigmentation, itching, burning, or stinging) graded at a level of 3 at any point in the study following the first application of study drug.
- The percent of subjects who experience a cutaneous adverse event (AE) irrespective of severity grade at any point in the study following the first application of study drug.
- Changes from baseline in all safety laboratory values and vital sign measurements as summarized using descriptive statistics by treatment group and study visit.
- Subjects will be assessed for the occurrence of new and ongoing AEs.

Cutaneous safety and tolerability will be evaluated by tabulations of AEs and Cutaneous Safety and Tolerability Evaluation scores (scaling, erythema, hypo/hyper-pigmentation, itching, burning, and stinging) to be assessed at each study visit. Itching, burning and stinging (cutaneous tolerability) will be reviewed with the subject at each study visit as an average over the period since the previous visit. Scaling, erythema, and hypo/hyper-pigmentation (cutaneous safety) will be assessed by the evaluator at each visit. Cutaneous tolerability signs and symptoms that result in the subject requiring a concomitant therapy, interruption of treatment, or discontinuation from the study will be reported as an AE.

Statistical Methods

All statistical processing will be performed using SAS® version 9.4 or later unless otherwise stated.

Statistical significance for superiority analyses will be based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less.

Non-inferiority of IDP-126 Gel to Epiduo® Forte will be assessed with 95% confidence intervals with the

following non-inferiority margins:

1) Absolute change from Baseline to Week 12 in inflammatory lesion counts: 2.1
2) Absolute change from Baseline to Week 12 in non-inflammatory lesion counts: 2.1
3) Percentage of subjects who achieve at least a two-grade reduction from baseline and are "Clear" or "Almost Clear" at Week 12 in the Evaluator's Global Severity Score: 10%

Confidence intervals and superiority testing of lesion counts will be based on an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate.

Confidence intervals and superiority testing of the dichotomized EGSS will be based on logistic regression with factors of treatment group and analysis center. The TSS will be recorded for applicable subjects with truncal acne, and will be summarized at Week 2, 4, 8, and 12, with the percentage of subjects achieving at least a 2-grade reduction from baseline included in the summary.

The primary method of handling missing efficacy data will be based on estimation using the method of Markov Chain Monte Carlo (MCMC) imputation. Other methods, as well as the MCMC imputation, will be specified in the statistical analysis plan which will be finalized prior to data base lock.

Populations Analyzed and Treatment Groups:

Inflammatory and non-inflammatory lesion counts will be recorded for each Subject at Baseline and at Weeks 2, 4, 8, and 12. The absolute and percent change from Baseline in inflammatory and non-inflammatory lesions will be derived for each Subject at Weeks 2, 4, 8, and 12.

The EGSS will be recorded for each Subject. The EGSS will be dichotomized into "success" and "failure" with a subject considered a success if the Evaluator's Global Severity Score at Week 2, 4, 8, and 12 is at least 2 grades less than baseline and Clear or Almost Clear.

Populations Analyzed:

An intent-to-treat (ITT) analysis will be conducted on all study subjects. The ITT population will consist of all randomized subjects who received study drug.

All subjects who are randomized and receive at least 1 confirmed dose of study drug will be included in the Safety population.

A per-protocol (PP) analysis will also be conducted. Subjects will be eligible for the PP analysis if they complete the 12-week evaluation without noteworthy study protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). The PP population will include subjects in the ITT population who do not meet any of the following criteria:

- Failed any of the inclusion/exclusion criteria.
- Have taken any interfering concomitant medications.
- Did not attend the Week 12 visit, with the exception of a discontinuation from the study due to an AE related to study treatment or documented lack of treatment effect.
- Missed more than 1 post baseline study visit prior to Week 12.
- Have not been compliant with the dosing regimen (i.e., subjects may not miss more than 5 consecutive days of dosing and must take 80%-120% of expected doses). The number of expected doses will be determined for each subject based on the length of their participation in the study.
- Out of visit window at the Week 12 visit.

Subjects who discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect (and/or worsening of condition) will be included in the PP population. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

Approximately 660 subjects will be randomized in a 2:2:1:1 ratio to the following treatment groups:

- 220 Subjects to IDP-126 Gel (clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15%)
- 220 Subjects to Epiduo® Forte Gel (adapalene 0.3%/BPO 2.5%)

- 110 Subjects to IDP-126 Vehicle Gel (stored at 2-8°C)
- 110 Subjects to IDP-126 Vehicle Gel (stored at controlled room temperature)

Subject demographic and baseline characteristics will be summarized by treatment group using descriptive statistics for the ITT, PP, and Safety analysis sets.

Efficacy Evaluation:

Primary efficacy analyses will be conducted on the ITT (primary) and PP (supportive) populations. Secondary analyses will be conducted on the ITT population.

Primary:

Co-primary efficacy analyses include the absolute change from baseline in inflammatory and in non-inflammatory lesions, and the dichotomized Evaluator's Global Severity Score. The pre-specified time point will be Week 12. All of the testing relating to the analysis of inflammatory and non-inflammatory lesions will use the methods introduced in Section 12.

Secondary:

Secondary efficacy endpoints include absolute and percent change in inflammatory and non-inflammatory lesion counts from baseline to Weeks 2, 4, 8, and 12 and also percentage of subjects with at least a two-grade improvement and are "clear" to "almost clear" in the Evaluator's Global Severity Score from baseline at each visit.

For subjects with truncal acne, percentage of subjects who have at least a 2-grade reduction at Week 2, 4, 8, 12 from Baseline in the TSS will be evaluated.

Safety Evaluation:

All subjects who are randomized and receive at least 1 confirmed dose of study drug will be included in the Safety population. Safety will be evaluated by tabulations of AEs, Cutaneous Safety and Tolerability Evaluations, vital signs/abbreviated physical examinations, and safety laboratory results.

Cutaneous Safety and Tolerability Evaluation scores (erythema, scaling, hypo/hyper-pigmentation, itching, burning, and stinging) will be presented with descriptive statistics at baseline and at Weeks 2, 4, 8, and 12 for each treatment group. Frequencies and percentages for each outcome category will be included in these statistics. Mean values will be presented graphically by week and treatment group.

Vital sign measurements, an abbreviated physical examination, and safety laboratory results will be conducted on all subjects at specified visits. For pre-menses females and FOCBP, urine pregnancy and serum pregnancy testing will occur at specified visits. Changes from baseline in safety laboratory values and vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits. Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at Baseline and Week 12. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment time point will also be provided.

Determination of clinical significance for all out-of-range laboratory values will be made by each investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

All previous and concomitant medications will be classified based on terminology from the World Health Organization Drug Dictionary. Previous therapies and concomitant medications data will be presented in the data listings.

All AEs occurring during the study will be recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Descriptions of AEs will include the date of onset, the date the AE ended, the severity of the AE, the relationship to study drug, the action taken regarding study drug usage, the action taken to treat the AE, and the outcome. Adverse events will be summarized by treatment group and severity. Each subject will be counted only once within a system organ class or a preferred term by using the AEs with the highest severity within each category.

Adverse events will be summarized by treatment group and relationship to study drug. Each subject will be counted only once within a system organ class or a preferred term by using the AEs with the greatest

relationship within each category.

Comparisons among treatment groups will be made by tabulating the frequency of subjects with one or more AEs (classified into MedDRA terms) during the study. The Fisher's Exact test will be used to compare the percentage of subjects in each treatment group who report any adverse event at a significance level of 0.05. The specific system organ classes and preferred terms analyzed will be those that are reported by at least one percent of the subjects in either active treatment group.

All information pertaining to AEs noted during the study will be listed by subject, detailing the verbatim descriptions given by the investigator, preferred term, system organ class, start date, stop date, severity, actions taken, and drug relatedness. The AE onset will also be shown relative (in number of days) to the day of initial dose of the randomized study drug. Serious adverse events (SAEs) will be tabulated by subject within treatment groups. In addition, a list of subjects who discontinued from the study and a list of subjects who experienced SAEs will also be provided.

Subject Self-Assessments

Subjects will be asked to complete an Acne-Specific Quality of Life Questionnaire during the study. The Investigator assessments (EGSS and lesion counts) will be conducted independently of this subject self-assessment. Inferential statistical analysis will not be performed on the questionnaire; the subjective responses will be compared between treatment groups for trends.

This study will be performed in compliance with Good Clinical Practice including the archiving of essential study documents. This protocol follows guidelines outlined by the International Conference for Harmonisation. All data furnished to the investigator and his/her staff, and all data obtained through this study, will be regarded as confidential and proprietary in nature and will not be disclosed to any third party, except for the United States Food and Drug Administration or other regulatory body, without written consent from the sponsor.

3 Table of Contents

LIST OF TABLES

4 List of Abbreviations and Definitions of Terms

Abbreviation or Specialist Term	Definition or Explanation
AE	Adverse event
BPO	Benzoyl peroxide
CBC	Complete Blood Count
cGCP	Current Good Clinical Practice
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Controlled Room Temperature
eCRF	Electronic case report form
EGSS	Evaluator's Global Severity Score
ET	Early termination
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	United States Food and Drug Administration
FOCBP	Female of Childbearing Potential
G	Gram
GCP	Good Clinical Practice
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
LED	Light Emitting Diode
MedDRA	Medical Dictionary for Regulatory Affairs
OTC	Over-the-counter
PDT	Photodynamic Therapy
PP	Per protocol
QoL	Quality of Life
RTSM	Randomization Trial Supply Management
SAE	Serious adverse event
TSS	Truncal Severity Score
UPT	Urine Pregnancy Test
WHO	World Health Organization

In this protocol, "sponsor duties" refer to responsibilities that will be performed by the sponsor, the sponsor's designee, or the sponsor's designated contract research organization (CRO). In this protocol, "investigator" refers to the principal investigator or his/her designee, who is responsible for performing the study procedures and assessments.

5 Introduction

Acne is a very common disorder of sebaceous follicles that is most prevalent among teenagers, usually triggered by the increase in androgen production occurring at puberty (Krakowski 2008). Although acne generally resolves by the age of 25, approximately 3% to 8% of adults 25 to 44 years of age present with acne (Goodman 2006, White 1998). The pathogenesis is complex and appears to involve 4 primary features: stimulation of sebum gland activity, bacterial proliferation (especially Propionibacterium acnes), abnormal follicular hyperkeratinization and resultant obstruction of the sebaceous follicles, and the release of inflammatory mediators (Thiboutot 2009). These changes in acne patients result in the formation of clinical inflammatory lesions including superficial pustules such as comedones (popularly known as “blackheads” or “whiteheads”) and more deeply located papules, nodules, and cysts (Krakowski 2008). The areas most affected by the disease include the pilosebaceous follicles of the head and upper trunk, where the sebaceous glands are particularly active (Webster 2002).

Given the complexity of the pathogenic mechanisms that lead to acne, for maximum efficacy, consensus guidelines recommend the use of combination therapy consisting of medications with different, but complementary, mechanisms of action (Thiboutot 2009). In particular, the guidelines advocate the use of a retinoid and an antibiotic (eg, clindamycin phosphate) or antibacterial (eg, benzoyl peroxide [BPO]) as first-line and maintenance therapy in patients with both inflammatory and non-inflammatory lesions (Ghali 2009, Thiboutot 2009).

Although antibiotics like clindamycin were among the first effective treatments for acne, recent acne management guidelines discourage the use of antibiotics as monotherapy due to the development of bacterial resistance (Nast 2012, Thiboutot 2009). The guidelines also recommend limiting both the frequency and duration of antibiotic use for acne, and to use antibiotics in conjunction with BPO to minimize the development of resistance at sites of application (Thiboutot 2009). Topically applied BPO is keratolytic, comedolytic, and anti-inflammatory, and has bactericidal activity against *Propionibacterium acnes* (Gollnick 2003, Harper 2010, Tanghetti 2009). To date, there is no evidence of *P acnes* resistance to BPO (Harper 2010). Further, the combination of BPO with chemical structures that contain a tertiary amine within their structure, such as clindamycin, increases the generation of BPO radicals and thereby creates a real biologic synergism (Burkhart 2008) that contributes to their complementary effects on acne pathogenesis.

Retinoids (eg, adapalene, tretinoin, tazarotene) are anticomedogenic, anti-inflammatory, and inhibit microcomedone formation (Ghali 2009, Zaenglein 2008). Topical, daily retinoid monotherapy is used to inhibit the formation of comedones and usually clear even severe comedonal acne within a few months (Shalita 2001). Adapalene, a synthetic retinoid, is a

naphthoic acid derivative with retinoid-like properties. In the cell, adapalene can bind specifically to retinoic acid nuclear (and not cytosolic) receptors to exert its effects (Zaenglein 2008). Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes (Piskin 2007). Topical formulations of adapalene have been used to treat acne in the United States (US) for more than 20 years.

Retinoids have also been paired with antibiotic/BPO fixed-dose combination products (Bowman 2005, Del Rosso 2007, Kircik 2007, Tanghetti 2006) and, consistently across studies of these products, regimens that included a topical retinoid were more effective than regimens that did not (Thiboutot 2009). Adapalene (0.1% gel and cream formulations) has a lower irritation potential relative to other retinoids (Dosik 2005a, Dosik 2005b) and is therefore well suited for use in combination topical regimens, particularly those containing BPO, which is also potentially irritating (Del Rosso 2007).

Thus, treatment with a combination of topical clindamycin phosphate, BPO, and adapalene can be expected to provide optimal overlapping benefits for maximal efficacy: each of these agents has some degree of anti-inflammatory activity; both the antibiotic and BPO decrease *P acnes* proliferation (Weiss 2004); BPO is also keratolytic (Harper 2010); and adapalene additionally regulates keratinization (Zaenglein 2008).

A fixed-dose combination treatment is optimal to enhance patient adherence due to simplified application regimens (eg, once daily versus sequential morning/evening administration of each active agent) and also to preclude substance incompatibilities due to application errors (eg, oxidation by using incompatible single agents) (Thielitz 2013). Of note, when an adapalene 0.1% gel and a clindamycin 1.2%/BPO 5% fixed-dose combination gel were combined in equal amounts by weight, there was no resultant instability of any of the active components for up to 24 hours (Bikowski 2006).

The current study is intended to evaluate the safety and efficacy of IDP-126 Gel, a novel fixed-dose combination of clindamycin phosphate, BPO, and adapalene (1.2%/3.1%/0.15%), relative to Epiduo® Forte Gel (0.3% adapalene / 2.5% BPO) and its vehicle (IDP-126 Vehicle Gel) for the treatment of acne vulgaris in subjects 12 years of age and older.

6 Study Objectives and Purpose

The objective of this study is to establish a clinical bridge for IDP-126 Gel to the comparator drug Epiduo® Forte Gel in subjects with moderate to severe acne vulgaris. The safety and efficacy of once daily application of IDP-126 Gel will be compared to Epiduo® Forte and IDP-126 Vehicle Gel.

7 Investigational Plan

7.1 Overall Study Design and Plan: Description

This is a multicenter, randomized, double-blind, vehicle-controlled, study designed to assess the safety, tolerability, and efficacy of IDP-126 Gel (clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15%) in comparison with Epiduo® Forte Gel (adapalene 0.3%/BPO 2.5%) and vehicle gel. To be eligible for the study, subjects must be at least 12 years of age or older, and have a clinical diagnosis of moderate to severe acne vulgaris (a score of 3 or 4 [moderate to severe] on the Evaluator's Global Severity Scale [EGSS]), presenting with 30-100 inflammatory facial lesions (papules, pustules, and nodules), 35-150 non-inflammatory facial lesions (open and closed comedones), and ≤ 2 facial nodules.

Approximately 660 subjects will be enrolled into this study and randomized into 1 of the following treatment groups in a 2:2:1:1 ratio:

- 220 subjects to receive IDP-126 Gel, once daily application
- 220 subjects to receive Epiduo® Forte Gel, once daily application
- 110 subjects to receive IDP-126 Vehicle Gel (stored at 2-8°C), once daily application
- 110 subjects to receive IDP-126 Vehicle Gel (stored at CRT), once daily application

Subjects will be enrolled at approximately 40 independent study centers. The duration of treatment will be 12 weeks. Subjects will be evaluated at Screening, Baseline, and at subsequent follow-up visits (Weeks 2, 4, 8, and 12).

A randomization trial supply management system (RTSM) will be employed to facilitate randomization of study subjects. Treatment assignments and study drug kit numbers will be generated centrally by the RTSM. At each study center, subject numbers will be assigned consecutively at the Screening visit, starting with 001.

The assigned study drug will be applied topically to the face once daily at home, in the evening, for 12 weeks (up to the evening prior to the Week 12 visit), with the exception of study visit days (Baseline, Week 2, 4 and 8) where study drug will be applied (also by the

subject) after the study visit is completed, at the investigational center. The initial application will be done at the investigational center as per instruction from the study coordinator or designee. The subjects will be instructed to avoid exposure to direct sunlight in order to prevent sunburn. Use of sunscreens with at least a sun protection factor (SPF) of 15 and protective clothing (eg, a hat) is recommended when exposure cannot be avoided. Subjects will apply their daily treatments at home as explained by the study coordinator or designee at each study center. During post baseline study visits (Weeks 2, 4, 8 and 12), the subjects will be asked to return their used pumps of study drug and will be dispensed new pumps of study drug (new pumps dispensed on Weeks 4 and 8 only; Week 2 will have no new study drug dispensed; and Week 12 will be final visit). During the study, each subject will only be permitted to use approved, non-medicated cleansers, moisturizers, and sunscreens.

Though not a requirement for study inclusion, the subject may be assessed for truncal acne (neck, upper chest, upper back and shoulders). If the subject presents with truncal acne and would like to apply study drug to these area(s), a separate evaluation will be performed to assess truncal acne using a Truncal Severity Score (TSS). TSS will be conducted at Baseline, Week 2, Week 4, Week 8, and Week 12. Subject participation in treatment of truncal acne is optional.

During the study, subjects will be asked to complete the Acne-Specific Quality of Life questionnaire (Acne-QoL, Appendix 17.3). The Investigator assessments (EGSS, lesion counts, and TSS as applicable) will be conducted independently of this subject self-assessment. The EGSS should be completed prior to the lesion counts. For subjects participating in the treatment of truncal acne, Investigators will only conduct the TSS, and lesions counts will not be conducted for truncal acne participants.

The Acne-QoL questionnaire will be completed at Baseline and Week 12. Inferential statistical analyses will not be performed on the questionnaire; the subjective responses will be compared between treatment groups for trends. Information on reported and observed adverse events (AEs) will be obtained at each visit. An abbreviated physical examination, along with vital sign measurements, will be performed at Baseline and Week 12 (end of study, final visit) for all subjects.

Blood samples will be collected from subjects at Baseline and Week 12 for CBC/Diff and serum chemistry. For all female subjects of childbearing potential (FOCBP), urine pregnancy testing will be performed at Screening, confirmed prior to randomization at Baseline, and then repeated at Weeks 2, 4, 8 and 12. Serum pregnancy test will also be conducted at Baseline and Week 12.

Subjects who terminate their study participation early will be asked to complete all Week 12 assessments, as appropriate. Subjects who discontinue from the study during the treatment period will not be replaced.

Table 1. Study Design and Schedule of Assessments

PROCEDURES	VISIT 1[a] Screening Visit (Day -35 to 0)	VISIT 2 Baseline Day 0	VISIT 3 Week 2 (Day 14 ±3 days)	VISIT 4 Week 4 (Day 28 ±3 days)	VISIT 5 Week 8 (Day 56 ± 3 days)	VISIT 6[b] Week 12 (Day 84 -3/+5 days)
Informed Consent/Assent	X					
Obtain Subject Number from RTSM	X					
Demographics	X					
Medical History[c]	X	X				
Inclusion/Exclusion Criteria[c]	X	X				
Previous Therapies[c]	X	X				
Acne-QoL		X				X
Pregnancy Test (pre-menses and FOCBP)[d]	X	X	X	X	X	X
Abbreviated Physical Examination[c,e]	X	X				X
Vital Sign Measurements[c]	X	X				X
Safety Labs (CBC/Diff, serum chemistry)		X				X
EGSS	X	X	X	X	X	X
Lesion Counts	X	X	X	X	X	X
TSS (if applicable)		X	X	X	X	X
Photographs (select study centers only, face only)		X		X	X	X
Cutaneous Safety Evaluation[f]		X	X	X	X	X
Tolerability Evaluation[f]		X	X	X	X	X
Randomization in RTSM (obtain kit #)		X		X	X	
Administer Subject Instructions (see Appendix 17.1)		X				
Dispense Study Drug		X		X	X	
Weigh Study Drug		X	X	X	X	X
Study Drug Applied at Study Center		X	X	X	X	
Study Drug Collected				X	X	X
Subject Diary Calendar Dispensed		X	X	X	X	
Subject Compliance Reviewed / Diary Reviewed			X	X	X	X
Adverse Events	X	X	X	X	X	X
Concomitant & Prohibited Therapies/Medication Review	X	X	X	X	X	X
End of Study						X

[a] If no washout is needed, Visits 1 and 2 may occur on the same day. If a washout is needed, Visit 2 must occur after the appropriate washout period.
[b] All Week 12 procedures must be completed for all subjects who terminate early.
[c] Update at Baseline visit prior to randomization.
[d] For pre-menses females and FOCBP, the urine pregnancy test must be completed at all scheduled visits. Serum pregnancy testing will be completed at Baseline and Week 12 only. Subjects with a positive pregnancy test at any time during the study will be discontinued.
[e] Height will be measured at Screening only; weight measurements and examinations of other abbreviated physical parameters will be performed at Baseline and Week 12.
[f] Cutaneous safety and tolerability will also be conducted (and recorded) for subjects participating in optional truncal acne application during the course of the study.

8 Selection and Withdrawal of Subjects

8.1 Subject Inclusion Criteria

Subjects meeting all of the following criteria will be eligible for study entry:

1. Male or female at least 12 years of age and older.
2. Written and verbal informed consent must be obtained. Subjects less than age of consent must sign an assent for the study and a parent or a legal guardian must sign the informed consent (if subject reaches age of consent during the study they should be re-consented at the next study visit).
3. Subject must have an EGSS of 3 (moderate) or 4 (severe) at the baseline visit.
4. Subjects with a facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 30, but no more than 100.
5. Subjects with a facial acne non-inflammatory lesion (open and closed comedones) count no less than 35, but no more than 150.
6. Subjects with 2 or fewer facial nodules.
7. FOCBP[1] and females who are premenses must be willing to practice effective contraception for the duration of the study. (Effective contraception is defined as stabilized on oral [either combined estrogen and progestogen containing or progestogen only] contraceptive for at least 3 months, intrauterine device/system, condom with spermicide, diaphragm with spermicide, implant, NuvaRing®, injection, transdermal patch, bilateral occlusion, vasectomized partner, or abstinence.) Females on birth control pills must have taken the same type pill for at least 3 months prior to entering the study and must not change type during the study. Those who have used birth control pills in the past must have discontinued usage at least 3 months prior to the start of the study. Women who use birth control for acne control only should be excluded.
8. Premenses females and FOCBP must have a negative urine pregnancy test[2] at the Screening Visit, and a negative urine pregnancy test at the Baseline Visit.
9. Subjects must be willing to comply with study instructions and return to the clinic for required visits. Subjects under the age of consent must be accompanied by the parent or legal guardian at the time of assent/consent signing.
10. If a cleanser, moisturizer or sunscreen is needed during the study, subjects must be willing to use only allowed cleansers, moisturizers, sunscreens, or moisturizer/sunscreen combination products (see Appendix 17.2). The subject must agree to use non-comedogenic products (including makeup and shaving products).

[1] Premenses females and FOCBP include any female who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea > 12 consecutive months; or women on hormone replacement therapy with documented plasma follicle-stimulating hormone level > 35mLU/mL). Even women who are using oral, implanted or, injectable contraceptive hormones, an intrauterine device, barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, practicing abstinence or where partner is sterile (eg, vasectomy), should be considered to be of child bearing potential.

[2] Urine pregnancy tests must have a minimum sensitivity of 25mIU HCG/mL of urine and must be performed within 72 hours prior to the start of study drug. Kits will be provided by the CRO/designee.

8.2 Subject Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Use of an investigational drug or device within 30 days of enrollment or participation in a research study concurrent with this study.
2. Any dermatological conditions on the face that could interfere with clinical evaluations such as acne conglobata, acne fulminans, secondary acne, perioral dermatitis, clinically significant rosacea, gram-negative folliculitis, dermatitis, eczema.
3. Any underlying disease(s) or some other dermatological condition of the face that requires the use of interfering topical or systemic therapy or makes evaluations and lesion count inconclusive.
4. Subjects with a facial beard or mustache that could interfere with the study assessments.
5. Subjects with more than two (2) facial nodules.
6. Evidence or history of cosmetic-related acne.
7. Subject has a history of experiencing significant burning or stinging when applying any facial treatment (eg, makeup, soap, masks, washes, sunscreens, etc) to their face.
8. Female subjects who are pregnant, nursing mothers, planning a pregnancy during the course of the study, or become pregnant during the study.
9. Use of estrogens (eg, Depogen, Depo-Testadiol, Gynogen, Valergen, etc) for less than 12 weeks immediately preceding study entry; subjects treated with estrogens 12 or more consecutive weeks immediately prior to study entry need not be excluded unless the subject expects to change dose, drug or discontinue estrogen use during the study.
10. If female, subject has a history of hirsutism, polycystic ovarian disease or clinically significant menstrual irregularities.
11. History of regional enteritis, ulcerative colitis, inflammatory bowel disease, pseudomembranous colitis, chronic or recurrent diarrhea, or antibiotic-associated colitis.
12. Treatment of any type of cancer within the last 6 months, with the exception of complete surgical excision of skin cancer outside the treatment area.
13. Subject uses medications and/or vitamins during the study which are reported to exacerbate acne (azathioprine, haloperidol, Vitamin D, Vitamin B12, halogens such as iodides or bromides, lithium, systemic or topical mid-to super-high potency corticosteroids on the treatment area, phenytoin and phenobarbital). Multivitamins, including Vitamin A, at recommended daily doses, and Vitamin D at stable doses, are acceptable.
14. History of hypersensitivity or allergic reactions to any of the study preparations as described in the Investigator's Brochure, including known sensitivities to any dosage form of clindamycin phosphate, BPO, or adapalene.

15. Concomitant use of potentially irritating over-the-counter products that contain ingredients such as BPO, alpha-hydroxy acid, salicylic acid, retinol or glycolic acids.
16. Subjects who have not undergone the specified washout period(s) for the following topical preparations / physical treatments used on the face or subjects who require the concurrent use of any of the following in the treatment area:

Topical astringents and abrasives on the face	1 week
Non-allowed moisturizers or sunscreens on the face	1 week
Antibiotics on the face	2 weeks
Other topical anti-acne drugs on the face	2 weeks
Soaps containing antimicrobials on the face	2 weeks
Anti-inflammatory agents and corticosteroids on the face	4 weeks
Retinoids, including retinol on the face	4 weeks
Chemical peel/microdermabrasion on the face	4 weeks
Light (e.g. LED, PDT) therapy on the face	4 weeks
Acne surgery	4 weeks
Laser therapy on the face	4 weeks

17. Subjects who have not undergone the specified washout period(s) for the following systemic medications or subjects who require the concurrent use of any of the following systemic medications:

Corticosteroids (including intramuscular injections) (inhaled corticosteroids are allowed)	4 weeks
Antibiotics	4 weeks
Other systemic acne treatments	4 weeks
Systemic retinoids	6 months

18. Subject intends to use a tanning booth or sunbathe during the study.
19. Subjects who are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
20. Subjects with any underlying disease that the investigator deems uncontrolled, and poses a concern for the subject's safety while participating in the study.

8.3 Subject Withdrawal Criteria

Reasons for withdrawal may include, but are not limited to, the following:

- Acne flare, as determined by the investigator, which requires treatment with a disallowed therapy.
- Either at the investigator's request, for tolerability reasons (eg, severe adverse reactions), or at the subject's request.
- When the requirements of the protocol are not followed.

- When a concomitant therapy likely to interfere with the results of the study is reported or required by the subject (the investigators will report all such information on the source documents/eCRFs and decide, in accordance with the Sponsor, whether the subject is to be withdrawn).
- When a subject is lost to follow-up. The investigators will try twice to reach the subject by telephone, email and/or text message, and will send a follow-up letter by certified mail before considering that the subject is lost to follow-up. These actions will be reported on the End of Study source documents and the final eCRF and a copy of the follow-up letter will be maintained in the investigator's file.

All premature discontinuations and their associated reasons must be carefully documented by the investigator on source documents and the final eCRF, and, if need be, on the AE form. In any case, no subject who has been included and has an assigned study number can be replaced by another if the subject discontinues prematurely for whatever reason. All data gathered on the subject prior to termination will be made available to the Sponsor.

Reasons for study completion/discontinuation as listed on the final report form are defined as follows:

Normal Study Completion – Subject completes the study as planned in the protocol.

Adverse Event – Complete an AE form.

Death – Complete a serious adverse event (SAE) form.

Subject Request – Consent withdrawal, subject moved, schedule conflicts.

Protocol Violation – Contact the Sponsor or designee before making decision.

Lost to Follow-Up – Document with 2 phone calls, emails and/or text messages, and a certified letter.

Pregnancy – Subject will discontinue study drug immediately, but will be followed to term. Complete a pregnancy form.

Worsening Condition – Subject requires alternate treatment for acne before the end of the study and the investigator determines it is not due to lack of efficacy.

Lack of Efficacy – Subject requires alternate treatment for acne after at least 2 weeks of study drug treatment and the risk of continuing the subject in the study outweighs the benefit as determined by the investigator.

Withdrawal by Parent/Guardian – An indication that the study participant has been removed from the study by the parent or legal guardian; includes consent withdrawal, subject moves, schedule conflicts, etc.

Study Terminated by Sponsor – An indication that a clinical study was stopped by its Sponsor.

Other – Specify in the comments section of the eCRF.

Subjects who terminate study drug early will be asked to complete all Week 12 assessments and procedures prior to commencement of any alternative therapy for acne (if possible). Subjects who discontinue from the study during the treatment period will not be replaced.

All subjects are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, and without prejudice. No constraints will be placed on ordinary subject management, and subjects, when appropriate, will be placed on other conventional therapy upon request or whenever clinically necessary as determined by their physician.

9 Treatment Plan

9.1 Methods of Assigning Subjects to Treatment Groups

This is a double-blind study in which the identity of the study drug will be unknown to the investigator/evaluator and all subjects, as well as all individuals closely associated with the study.

Eligible subjects will be randomized to 1 of the 4 study drug groups in a ratio of 2:2:1:1 (IDP-126 Gel : Epiduo® Forte Gel : IDP-126 Vehicle Gel (stored at 2-8°C) : IDP-126 Vehicle Gel (stored at CRT)).

The study center will assign each screened subject a unique 6-digit study subject number. The number will consist of the 3-digit study center number (pre-assigned by Sponsor/designee) and the 3-digit chronological screening number, starting with 001 (eg, 101001, 101002). The randomization system will assign the study drug kit to subjects based on a randomization code; the kit will be dispensed to the subjects at Baseline and Weeks 4 and 8 by the study center staff. A study drug log will document the inventory, dispensing, and collecting of study drug at each study center.

9.2 Randomization and Blinding

The study drugs will be packaged and labeled, and the study drug kits will be numbered sequentially and dispensed randomly to the subjects entering the study within each study center. Study drug supplies will be distributed to the study centers to maintain the randomization ratio within each study center.

As a double-blind study, the investigators/evaluators, the study center staff, the Sponsor, and the clinical monitors will not be aware of the treatment assigned to the individual study subjects. Delegated staff members at each study center will dispense the study drugs and will collect all used and unused study drug pumps as scheduled.

9.3 Unblinding

The treatment assignments for all enrolled subjects will be unblinded only after the conclusion of the study. Specifically, the blind will be broken only after all data are entered into the database,

verified, and validated; subject evaluability assessments are performed and the database is locked.

In the case of a medical emergency, the investigator can break the blind for the subject involved, preferably by first discussing the situation with the medical monitor and the Sponsor (or designee) immediately. After confirmation, the investigator will be contacted with unblinding information by a Sponsor representative or via the RTSM. The investigator will record the code break in the subject's source documents.

9.4 Prior and Prohibited Concomitant Medication or Therapy

Any concomitant medication or therapy stopped for washout as indicated below is to be recorded. As noted in the exclusion criteria, there are mandatory washout periods and restrictions during the study for the following topical treatments/physical treatments on the face that have a known beneficial effect for acne vulgaris:

Topical astringents and abrasives on the face	1 week
Non-allowed moisturizers or sunscreens on the face	1 week
Antibiotics on the face	2 weeks
Other topical anti-acne drugs on the face	2 weeks
Soaps containing antimicrobials on the face	2 weeks
Anti-inflammatory agents and corticosteroids on the face	4 weeks
Retinoids, including retinol on the face	4 weeks
Chemical peel/microdermabrasion on the face	4 weeks
Light (e.g. LED, PDT) therapy on the face	4 weeks
Acne surgery	4 weeks
Laser therapy on the face	4 weeks

In addition, there is a mandatory washout period and restriction on use during the study for the following systemic drugs:

Corticosteroids (including intramuscular injections; inhaled corticosteroids are allowed)	4 weeks
Antibiotics	4 weeks
Other systemic acne treatments	4 weeks
Systemic retinoids	6 months

Subjects using concomitant therapies during the course of the study that could interfere with the interpretation of the study results (including, but not limited to, those listed above) should not be withdrawn, but the use of the concomitant product should be discontinued. Examples of products/procedures that are prohibited during the course of the study include (but not limited to) acne surgery, use of comedone removal strips, and use of comedogenic products (makeup, shaving products). With the exception of the study drug and the treatments listed above, no other topical/physical treatment for acne will be permitted.

Information on concomitant medications or therapies will be recorded in the Prior and Concomitant Medication or Therapy source document and eCRF. Any therapy used by the subject will be considered concomitant therapy (e.g., facial procedures, surgical procedures, investigations, and operations), and any medication, both over-the-counter (OTC) or prescription, used by the subject will be considered concomitant medication (eg, aspirin, Tylenol, birth control pills, vitamins). Every attempt should be made to keep concomitant medication / therapy dosing constant during the study. Any change to concomitant medication / therapy should be noted on the Concomitant Therapy or Medication source document and eCRF.

All cleansers, moisturizers, sunscreens and other topical products used on the treatment area that are not medicated will be captured on the Prior and Concomitant Therapy source document and eCRF. Subjects must use investigator-approved, non-medicated cleansers, moisturizers, and sunscreens.

Subjects should avoid excessive ultraviolet (UV) exposure by such activities as sunbathing or tanning booths. Use of sunscreens with at least SPF 15 and protective clothing during the day (eg, a hat) are recommended when exposure cannot be avoided.

9.5 Treatment Compliance

Each subject will be instructed on the importance of returning his or her study drug at each applicable study visit. If a subject does not return his or her study drug at a particular study visit, he or she will be instructed to return it as soon as possible. The subjects will bring the pump(s) dispensed at each specified study visit to the next subsequent study visit. Each pump will be weighed on a calibrated scale (with the cap on, and to the nearest tenth of a gram) by a study coordinator or designee prior to dispensing and after collecting. The subject will also be asked to complete a diary calendar and will be questioned regarding study drug use since the previous visit in order to judge the subject's compliance with applying the study drug. A subject who deviates meaningfully from the prescribed application amount will be counseled. Any missed applications of study drug will be noted by the subject on the diary, which will be collected and placed in the appropriate source document. Missed applications will be documented in the eCRF.

9.6 Protocol Deviations and Violations

The investigators must read the protocol thoroughly and must follow the instructions exactly.

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and agreed to by the investigator. Deviations usually have an impact on individual subjects or a small group of subjects and do not involve inclusion/exclusion or primary endpoint criteria.

A protocol violation occurs when there is non-adherence to the protocol that results in a substantial, additional risk to the subject, when the subject or investigator has failed to adhere to

critical protocol requirements (eg, inclusion/exclusion criteria), or when there is non-adherence to FDA regulations, ICH GCP guidelines, and local regulatory requirements.

Important protocol deviations impacting the safety of the subject or integrity of the study must be reported by the Investigator to the Sponsor, IRB/IEC, and regulatory authorities as applicable. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB/IEC and regulatory authorities.

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation or protocol change to eliminate an immediate hazard to a study subject without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) to prevent future occurrences, should be submitted to the IRB/IEC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

10 Study Drug Materials and Management

The study drug will be dispensed by an appropriately qualified member of the study staff assigned by the investigator to this task.

10.1 IDP-126 Gel, Epiduo® Forte Gel, and IDP-126 Vehicle Gel

The chemical names, chemical classes, and therapeutic classes of the active ingredients in IDP-126 Gel, Epiduo® Forte Gel and IDP-126 Vehicle Gel are listed in Table 2. Information regarding the study drugs is presented in Table 3.

Table 2. Drug Substances Identification

Established Name	**Clindamycin Phosphate**
Chemical Name	Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-**α**-D-galactooctopyranoside 2-(dihydrogen phosphate).
Chemical Class	Lincosamide antibiotic
Therapeutic Class	Anti-acne

Established Name	**Benzoyl Peroxide**
Chemical Name	Peroxide, Dibenzoyl
Chemical Class	Peroxide
Therapeutic Class	Anti-acne

Established Name	Adapalene
Chemical Name	(6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid)
Chemical Class	Synthetic retinoid
Therapeutic Class	Anti-acne

Table 3. Study Drug Identification

	Investigational Products			
	IDP-126 Gel	**IDP-126 Vehicle Gel-Refrigerated Stored at 2-8 °C**	**IDP-126 Vehicle Gel-Room Temperature Stored at CRT (Controlled Room Temperature)**	**Epiduo® Forte Gel**
Name of Active Ingredient	Clindamycin phosphate, BPO, and adapalene, USP	None	None	Adapalene and BPO, USP
Drug Name / Formulation/ Concentration	Clindamycin phosphate 1.2%/BPO 3.1%/ adapalene 0.15%, Gel	IDP-126 Vehicle Gel	IDP-126 Vehicle Gel	Adapalene 0.3% / BPO 2.5%
Manufacturer	Bausch Health Companies Inc. 2150 St. Elzear Blvd West, Laval (Quebec), Canada H7L 4A8			Galderma
Packaging	White Pump with weight range between 45g and 50g			
Storage Requirements	Store at 2-8 °C (36-46°F) prior to dispensing. Once dispensed, the product should be stored at room temperature up to 25°C (77°F) and assigned a 5-week use-by date. Do not freeze.		Store at 20°–25°C (68°–77°F), with excursions permitted to 15° to 30°C (59° to 86°F). Once dispensed to the subject, assign a 5-week use-by date. Do not freeze.	
Appearance	Opaque white to off-white gel			Opaque white to very pale yellow gel
Dosing Schedule	Once daily × 12 weeks			
Route of Administration	Topical Application			

10.1.1 Packaging and Labeling

IDP-126 Gel, Epiduo® Forte Gel, and IDP-126 Vehicle Gel will be supplied in subject kits. The IDP-126 Vehicle Gel will be two separate treatment arms: one arm will be refrigerated and stored at 2-8°C (36-44°F) prior to dispensation and the other arm will be stored at Controlled Room Temperature (CRT). Instructions will be provided to the designated study drug technician at each study center. When a subject is randomized into the study, the RTSM-specified kit number will be assigned to be used for that randomized subject. Each subject kit will contain one pump, containing 45-50g of study material. One pump will be dispensed to the subject at each dispensing visit: Baseline, Week 4, and Week 8. Each pump will be weighed on a calibrated scale, prior to dispensing (with the cap on, and to the nearest tenth of a gram). After weighing the

pump and prior to first use of the study drug pump, the pump will need to be actuated approximately 10 times until the gel begins to dispense. The pump is actuated by depressing the pump head using one or two fingers. This is to remove the air from the pump prior to product dispensing and is known as "priming the pump". Priming the pump must occur at each dispensing visit (or if/when a replacement pump is issued).

The subject will bring the pump to the next study visit (Week 2), where it will be collected and weighed (with the cap on, and to the nearest tenth of a gram) – a new pump will not be dispensed at this visit, and the original pump will be returned to the subject. The subject will then bring the same pump to the subsequent study visit (Week 4), where it will be collected and weighed (with the cap on) to the nearest 0.1 gram; one new pump will be dispensed again by the RTSM at Week 4, weighed (with the cap on) to the nearest 0.1 gram and provided to the subject. The same will occur at the Week 8 visit. If the subject loses a pump (lost or damaged pump), another kit will be dispensed via RTSM under an unscheduled visit. When weighing the subject's returned pump, if the cap is missing, a cap should be borrowed from another pump for weighing purposes; after weighing the pump with the borrowed cap, the cap should be returned to its original pump. All used and unused study drug pumps will be collected and weighed at the final study visit (Week 12). All dispensing and collecting of study drug pumps will be documented on the study drug accountability log.

Study drug will be packaged and labeled in a manner consistent with study design. Study drug will be labeled according to applicable country and regional regulations for an investigational drug.

10.1.2 Storage, Handling, and Disposal of Study Drug

At the investigational center, the IDP-126 Gel and IDP-126 Vehicle Gel (Refrigerated) should be stored at 2°C to 8°C (36°F to 46°F) and should not be frozen. Once opened and dispensed to the subject, the study drug should be stored at room temperature up to 25°C (77°F). Epiduo® Forte Gel and IDP-126 Vehicle Gel (Room Temperature) should be stored at 20°–25°C (68°–77°F), with excursions permitted to 15° to 30°C (59° to 86°F) and should not be frozen. Once opened and dispensed to the subject, assign a 5-week use-by date.

Once a kit has been assigned to a subject, the kit should be pulled from pre-dispensing storage conditions, and kept in the secure drug storage area by an unblinded dispenser for approximately 10 to 15 minutes before dispensing to the subject. All empty, partially used and unused study drug will be returned to the Sponsor or designee upon study completion of the study for documented disposal.

10.1.3 Administration

For all subjects, the study drug will be applied topically to the face once daily at home in the evening, at least 30 minutes before bedtime, for a period of 12 weeks, with the exception of study visit days (Baseline, Week 2, 4, and 8) where study drug will be applied by the subject

after the study visit is completed at the investigational center. For the subset of subjects who will be treating truncal (neck, upper chest, upper back and shoulders) acne (optional), they should follow the same instructions as noted for the face. The study drug will be applied as a thin coating that is gently rubbed into the skin. Study drug use will be limited to the face, and truncal areas (if applicable).

The investigator and/or trained study center staff member will instruct the subject on the proper study drug application procedure during the Baseline visit (see Appendix 17.1). All subjects will be instructed to apply the study drug at approximately the same time every day for 12 weeks, after cleansing with an investigator-approved cleanser. On study visit days (Baseline, Weeks 2, 4, and 8) subjects should be instructed to wait until the end of their study visit to apply study medication at the investigational site (note, this will affect evening application times on study visit days, which is acceptable. Subjects should not apply another dose of study drug in the evening on the study visit days). No time interval between dosing and meals or any other activity is specified. Study center personnel oversight of a subject's on-site application of study drug is required at Baseline, Week 4 and Week 8, to ensure training/reinforcement of proper application technique.

During daily application, subjects will be instructed to gently wash their faces with an investigator-approved, non-medicated cleanser and warm (not hot) water. After washing, the subjects will be asked to thoroughly rinse and gently pat their faces dry. The subjects should use the pump to dispense one pea size amount of the study drug onto the fingertip. The study drug gel should be dotted onto 6 areas of the face: the chin, left cheek, right cheek, nose, left forehead, and right forehead. After distributing the gel in this manner, the subject should gently rub the gel into the skin. This amount of drug should be sufficient to cover the entire face excluding the mouth, eyes, inside the nose, and lips. It is important for the subject to treat their entire face (excluding the mouth, eyes and lips) and they should be instructed NOT to treat only specific lesions. The subjects should gently smooth the study drug over the face evenly. The study drug should become invisible almost immediately following application with gentle rubbing. If this does not happen, the investigator should instruct the subject on the use of a smaller dosage. The subject should wash his/her hands after applying the study drug to the face. Subjects should also be instructed to place the cap back onto the pump after every use.

For subjects applying the study drug to the truncal area, the subjects or their designee (parent/legal guardian) will be instructed to cleanse the area gently before application of the study drug. The subjects should continue to use the pump to dispense one pea size amount onto the fingertip. The study drug should be spread in a thin layer across the truncal area (neck, upper chest, upper back and shoulders). It is important that the study drug is spread evenly, and specific lesions are not treated. The study drug should become invisible almost immediately following application with gentle rubbing. If this does not happen, the investigator should instruct the subject on the use of a smaller dosage. The subject should wash his/her hands after applying the

study drug. Subjects should also be instructed to place the cap back onto the pump after every use.

At each study visit, study staff will review the subject instructions for application of study drug to ensure proper use and compliance with application. The subjects will be instructed to continue using the same investigator-approved, non-medicated facial cleanser, moisturizer, and sunscreen, and not to change products during the study. At each visit, subjects are to be asked if they have changed their cleansing routine. Facial makeup may be applied according to the subject's normal daily routine; however, subjects should be instructed not to wear makeup during study visits as it may interfere with the evaluator's assessments. Subjects must also agree to use non-comedogenic makeup during the study if they use makeup. No other products should be used in the treatment area. Subjects should be instructed to minimize sun exposure and to use investigator-approved, non-medicated sunscreens of at least SPF 15 and to wear protective clothing during the day (eg, a hat) if exposure cannot be avoided.

Subjects should be instructed to store the study drug at room temperature. If a subject loses or misplaces the pump cap at any point during the study, the subject should contact the study center to return the exposed pump and receive a replacement pump.

10.2 Study Drug Accountability

Upon receipt of the study drug, the investigator is responsible for ensuring that the designated study center staff member will conduct a complete inventory of the study drugs and assume responsibility for their appropriate storage and dispensing. In accordance with federal regulations, the investigators must agree to keep all study drugs in a secure location with restricted access. The investigator will keep a record of the inventory, dispensing, and collecting of all study drugs. This record will be made available to the Sponsor's monitor for the purpose of accounting for all study drugs. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the investigators will be accounted for and, in no case, used in any unauthorized situation. Pumps will be weighed on a calibrated scale (with the cap on, and to the nearest tenth of a gram) before dispensing to and upon return by the subjects, and weights will be recorded on the pharmacy log and appropriate eCRF. All used and unused supplies will be returned to Sponsor/designee for destruction at the conclusion of the study. If a subject loses/misplaces a cap, the pump should still be weighed using a cap from another pump/kit.

11 Study Procedures and Evaluations

All subject information and data obtained during the study visits will be recorded in the source documents, applicable study logs, and eCRFs.

Evaluators must have appropriate, documented experience and training, or obtain approval from the Sponsor based on experience (or through additional training organized by the Sponsor).

At each study visit, every attempt should be made to ensure that the same investigator/evaluator assesses the same subject.

11.1 Schedule of Evaluations and Procedures

11.1.1 Visit 1: Screening Visit (Day −35 to Day 0)

The following procedures will be conducted at this visit:

1. Obtain written informed consent prior to performing any study procedures. Subjects less than the age of consent must sign an assent form, and the parent or legal guardian must sign the informed consent form.
2. Assign the subject a 6-digit subject number by accessing RTSM. The number will consist of the 3-digit study center number (pre-assigned to your study center) and the 3-digit sequential order screening number assigned by the RTSM (eg, 101001, 101002; in this example study center number is 101).
3. Record the subject's demographic information.
4. Record the subject's medical history.
5. Record all previous medications (including acne medications) used for the past 4 weeks (past 6 months for systemic retinoids). Record any therapies that will be used concomitantly during the study.
6. Perform an abbreviated physical examination, including height and weight, and measure vital signs (blood pressure, heart rate, respiration rate, and oral temperature). Note: height will only be measured at Screening, and not at subsequent study visits.
7. Assess the subject using the EGSS, followed by inflammatory and non-inflammatory lesion counting to determine eligibility.
8. Perform a urine pregnancy test for all females who are premenses and FOCBP. The urine pregnancy tests will be supplied by the CRO/designee.
9. Verify that the subject meets the applicable inclusion/exclusion criteria as outlined in Sections 8.1 and 8.2.
10. Discuss allowed cleansers, moisturizers, and sunscreens, and record any cleanser, moisturizer, and sunscreen use (Appendix 17.2).
11. If subject wears makeup, remind the subject not to wear makeup during any future visits.
12. If the subject requires a washout, schedule the Baseline visit to occur after the washout is complete. If no washout is required, the Screening and Baseline visits may occur on the same day.
13. Schedule the subject to return for the Baseline/Day 0 visit. If the subject requires a washout, schedule the Baseline/Day 0 visit to occur after the washout is complete.

NOTE: At the Baseline and Week 12 visits, serum pregnancy testing is **mandatory** for all premenses females and FOCBP. A urine pregnancy test must be completed at all scheduled study visits. The decision may be made by the investigator to do additional pregnancy tests during the course of the study.

11.1.2 Visit 2: Baseline Visit (Day 0)

If a washout is not needed, this visit may occur on the same day as the Screening Visit (Visit 1). If a washout is needed, Visit 2 (Baseline) must occur after the appropriate washout period based on the criteria provided in Section 8.2.

The following procedures will be conducted at this visit:

1. The baseline Acne-QoL questionnaire will be completed by the subject and collected prior to conducting any other study-related procedures.
2. Verify that the subject continues to meet the applicable inclusion/exclusion criteria as outlined in Sections 8.1 and 8.2.
3. Record any changes in medical history since screening.
4. Record changes in any concomitant medications or therapies since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant medications / therapies as per Section 9.4.
5. Perform a urine pregnancy test for all females who are premenses and FOCBP. The urine pregnancy tests will be supplied by the CRO/designee.
6. Perform an abbreviated physical examination, including measurements of weight and vital signs (blood pressure, heart rate, respiration rate, and oral temperature). Any abnormal physical examination findings will be recorded.
7. The evaluator will perform the Baseline efficacy evaluations including an assessment based on the EGSS, and counts of inflammatory and non-inflammatory lesions. The EGSS is performed prior to the lesion counting. Every effort should be made for the same qualified, validated evaluator to perform the efficacy evaluations at all visits from Baseline to Week 12 for the same subject.
8. If the subject presents with truncal acne and agrees to have their study drug applied to these areas, then TSS will be performed from Baseline to Week 12. Note: lesion counts will not be performed for truncal acne.
9. The evaluator will perform the Cutaneous Safety and Tolerability Evaluations. If the subject presents with truncal acne and agrees to have their study drug applied to these areas, then the Cutaneous Safety and Tolerability Evaluations will also be performed for these areas.
10. Collect blood samples for routine laboratory analysis (CBC/Diff, serum chemistry, and serum pregnancy for pre-menses females and FOCBP).
11. *Select Sites Only* – Obtain representative photographs of the face.
12. Assign the subject the appropriate kit number (this number will be generated from the RTSM).
13. Once a kit has been assigned to a subject, the kit should be pulled from pre-dispensing storage conditions, and kept in the secure drug storage area by an unblinded dispenser for approximately 10 to 15 minutes before dispensing to the subject.

14. The study coordinator or designee will weigh a pump from the assigned kit and dispense it to the subject. The pump will be weighed (with the cap on) using a calibrated scale. Record the weight of the pump to the nearest 0.1 g. A study diary calendar will also be dispensed and the subject will be instructed to bring it to all subsequent visits.
15. The study coordinator or designee will instruct the subject on the proper application procedure for the study drug per Section 10.1.3, and will provide written subject use instructions to the subject (Appendix 17.1). For the first application, the subject will apply the study drug at the study center under the direction of the study coordinator or designee. The study drug should be applied **after** all clinical assessments. The study coordinator or designee will instruct the subjects to apply the study drug once daily at home at the same time of day, and will instruct the subject to use an investigator-approved, non-medicated sunscreen of at least SPF 15, and to wear protective clothing during the day (eg, a hat) if exposure cannot be avoided.
16. Record any AEs or changes in AEs since the screening visit and/or reported spontaneously by the subject.
17. Schedule the next study visit at Week 2 (Day 14 ± 3 days). Remind the subject not to apply study drug on day of next study visit.

    NOTE: At the Baseline and Week 12 visits, serum pregnancy testing is **mandatory** for all pre-menses females and females of childbearing potential.

11.1.3 Visit 3: Week 2 (Day 14 ± 3 Days) Visit

The following procedures will be conducted at this visit (if a subject terminates early, all final visit [Week 12/Final Visit] procedures must be performed):

1. The evaluator will perform the efficacy evaluations including the EGSS, inflammatory and non-inflammatory lesion counts. The EGSS is performed prior to the lesion counting. Every effort should be made for the same qualified and validated evaluator to perform the efficacy evaluations at all visits from Baseline to Week 12 for the same subject.
2. For subjects who are applying study drug to truncal acne, the TSS will be performed. Note: lesion counts will not be performed for truncal acne.
3. The evaluator will perform the Cutaneous Safety and Tolerability Evaluations. For subjects who are applying study drug to truncal acne, then the Cutaneous Safety and Tolerability Evaluations will also be performed for these areas.
4. Record changes in any concomitant medications / therapies since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant medications / therapies as per Section 9.4.
5. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
6. Perform a urine pregnancy test for all females who are premenses and FOCBP. The urine pregnancy tests will be supplied by the CRO/designee.
7. The study coordinator or designee will retrieve and weigh the used study drug pump. Record the weight of the pump (with the cap on) to the nearest 0.1 g. Note: a new pump

will **NOT** be dispensed at this visit. The original pump will be re-dispensed back to the subject.

8. The study diary calendar will be collected and reviewed for compliance. Any missed doses or deviations should be reported. A new study diary calendar will be dispensed.
9. The study coordinator or designee will remind the subject of the proper technique for application of study drug (Section 10.1.3). At this visit, the subject will apply the study drug at the study center under the direction of the study coordinator or designee to confirm proper technique. Any necessary retraining can be completed. The study drug should be applied **after** all clinical assessments. The study coordinator or designee will remind the subjects to apply the study drug once daily at home in the evening up to the evening prior to the Week 12 visit (study drug will not be applied in the evening after this study visit).
10. The study coordinator will instruct the subject to use a Sponsor/investigator-approved, non-medicated sunscreen of at least SPF 15, and to wear protective clothing during the day (eg, a hat) if exposure cannot be avoided.
11. Schedule the next study visit at Week 4 (Day 28 ± 3 days). Remind the subject to not apply study drug on day of next study visit, prior to the clinic visit.

11.1.4 Visit 4: Week 4 (Day 28 ± 3 Days) Visit

The following procedures will be conducted at this visit (if a subject terminates early, all final visit [Week 12/Final Visit] procedures must be performed):

1. The evaluator will perform the efficacy evaluations including the EGSS, inflammatory and non-inflammatory lesion counts. The EGSS is performed prior to the lesion counting. Every effort should be made for the same qualified and validated evaluator to perform the efficacy evaluations at all visits from Baseline to Week 12 for the same subject.
2. For subjects who are applying study drug to truncal acne, the TSS will be performed. Note: lesion counts will not be performed for truncal acne.
3. The evaluator will perform the Cutaneous Safety and Tolerability Evaluations. For subjects who are applying study drug to truncal acne, then the Cutaneous Safety and Tolerability Evaluations will also be performed for these areas.
4. Record changes in any concomitant medications / therapies since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant medications / therapies as per Section 9.4.
5. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
6. Perform a urine pregnancy test for all females who are premenses and FOCBP. The urine pregnancy tests will be supplied by the CRO/designee.
7. The study coordinator or designee will collect/retrieve and weigh the used study drug pump (with the cap on) to the nearest 0.1 g. Assign the subject a new kit number (i.e., the number that was generated by the RTSM). Once a kit has been assigned to a subject, the kit should be pulled from pre-dispensing storage conditions, and kept in the secure drug storage area by an unblinded dispenser for approximately 10 to 15 minutes before

dispensing to the subject. The new pump will be weighed (with the cap on) using a calibrated scale. Record the weight of the pump to the nearest 0.1 g.

8. The study diary calendar will be collected and reviewed for compliance. Any missed doses or deviations should be reported. A new study diary calendar will be dispensed.
9. *Select Sites Only* – Obtain representative photographs of the face.
10. The study coordinator or designee will remind the subject of the proper technique for application of the study drug (Section 10.1.3). At this visit, the subject will apply the study drug at the study center under the direction of the study coordinator or designee to confirm proper technique. Any necessary retraining can be completed. The study drug should be applied **after** all clinical assessments. The study coordinator or designee will remind the subjects to apply the study drug once daily at home in the evening up to evening prior to Week 12 visit (study drug will not be applied in the evening after this study visit).
11. The study coordinator will instruct the subject to use a Sponsor/Investigator-approved, non-medicated sunscreen of at least SPF 15, and to wear protective clothing during the day (eg, a hat) if exposure cannot be avoided.
12. Schedule the next study visit at Week 8 (Day 56 ± 3 days). Remind the subject to not apply study drug on day of next study visit, prior to the clinic visit.

11.1.5 Visit 5: Week 8 (Day 56 ± 3 Days) Visit

The following procedures will be conducted at this visit (if a subject terminates early, all final visit [Week 12/Final Visit] procedures must be performed):

1. The evaluator will perform the efficacy evaluations including the EGSS, inflammatory and non-inflammatory lesion counts. The EGSS is performed prior to the lesion counting. Every effort should be made for the same qualified and validated evaluator to perform the efficacy evaluations at all visits from Baseline to Week 12 for the same subject.
2. For subjects who are applying study drug to truncal acne, the TSS will be performed. Note: lesion counts will not be performed for truncal acne.
3. The evaluator will perform the Cutaneous Safety and Tolerability Evaluations. For subjects who are applying study drug to truncal acne, then the Cutaneous Safety and Tolerability Evaluations will also be performed for these areas.
4. Record changes in any concomitant medications / therapies since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant medications / therapies as per Section 9.4.
5. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
6. Perform a urine pregnancy test for all females who are premenses and FOCBP. The urine pregnancy tests will be supplied by the CRO/designee.
7. The study coordinator or designee will collect/retrieve and weigh the used study drug pump (with the cap on) to the nearest 0.1 g. Assign the subject a new kit number (i.e., the number that was generated by the RTSM). Once a kit has been assigned to a subject, the

kit should be pulled from pre-dispensing storage conditions, and kept in the secure drug storage area by an unblinded dispenser for approximately 10 to 15 minutes before dispensing to the subject. The new pump will be weighed (with the cap on) using a calibrated scale. Record the weight of the pump to the nearest 0.1 g.

8. The study diary calendar will be collected and reviewed for compliance. Any missed doses or deviations should be reported. A new study diary calendar will be dispensed.
9. *Select Sites Only* – Obtain representative photographs of the face.
10. The study coordinator or designee will remind the subject of the proper technique for application of the study drug (Section 10.1.3). At this visit, the subject will apply the study drug at the study center under the direction of the study coordinator or designee to confirm proper technique. Any necessary retraining can be completed. The study drug should be applied **after** all clinical assessments. The study coordinator or designee will remind the subjects to apply the study drug once daily at home in the evening up to evening prior to Week 12 study visit (study drug will not be applied in the evening after this study visit).
11. The study coordinator will instruct the subject to use a Sponsor/Investigator approved, non-medicated sunscreen of at least SPF 15, and to wear protective clothing during the day (eg, a hat) if exposure cannot be avoided.
12. Schedule the next study visit at Week 12 (Day 84 -3/+5 days). Remind the subject to not apply study drug on day of next study visit, prior to the clinic visit.

11.1.6 Visit 6: Week 12 (Day 84 -3/+5 Days) Visit – End of Study Visit

The following procedures will be conducted at this visit:

1. The Acne-QoL questionnaire will be completed by the subject and collected prior to any other study related procedures.
2. Perform an abbreviated physical examination, including measurements of weight and vital signs (blood pressure, heart rate, respiration rate, and oral temperature). Any abnormal physical examination findings will be recorded.
3. The evaluator will perform the efficacy evaluations including the EGSS, inflammatory and non-inflammatory lesion counts. The EGSS is performed prior to the lesion counting. Every effort should be made for the same qualified and validated evaluator to perform the efficacy evaluations at all visits from Baseline to Week 12 for the same subject.
4. For subjects who are applying study drug to truncal acne, the TSS will be performed. Note: lesion counts will not be performed for truncal acne.
5. The evaluator will perform the Cutaneous Safety and Tolerability Evaluations.
6. Record changes in any concomitant medications / therapies since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant medications / therapies as per Section 9.4.
7. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.

8. The study diary calendar will be collected and reviewed for compliance. Any missed doses or deviations should be reported.
9. The study coordinator or designee will retrieve all study drug (pump[s]) from the subject and weigh the pump(s) using a calibrated scale. The weight of the pump(s) (with the cap on) should be recorded to the nearest 0.1 g.
10. Perform a urine pregnancy test for all females who are premenses and FOCBP. The urine pregnancy tests will be supplied by the CRO/designee.
11. Collect blood samples for routine laboratory analysis (CBC/Diff, serum chemistry, and serum pregnancy for all pre-menses females and FOCBP).
12. *Select Sites Only* – Obtain representative photographs of the face.
13. Exit the subject from the study and complete the end of study eCRFs.

11.2 Evaluation of Efficacy

The determination of efficacy will be based on evaluator-blinded assessments of the signs and symptoms of acne vulgaris. Evaluators must be a board-certified/board-eligible dermatologist or have appropriate documented experience and training, and be present for formal study training and validation at the Investigator Meeting (and/or Site Initiation Visit), or obtain a waiver from the Sponsor based on experience (or through additional training organized by the Sponsor).

The EGSS assessments and lesion counts will be performed at each study visit. The EGSS assessments will be collected *before* the lesion counts. All subject assessments will be performed by a trained and validated evaluator. Every effort should be made to have the same evaluator assess the same subject at each visit. If this is not possible, the same evaluator should assess the subject at both the Baseline and Week 12 visits. If applicable, a separate TSS assessment and score will be collected and recorded for truncal acne at all study visits, starting at Baseline.

11.2.1 Evaluator's Global Severity Score (EGSS) and Truncal Severity Score (TSS)

The EGSS will be a static assessment that is independent of the baseline score. The investigator will make the assessment without referring to the baseline value. Every effort should be made for the same evaluator to perform each study assessment for the same study subject, for consistency in evaluations.

Subjects are eligible if they have acne vulgaris with a global severity of 3 (moderate) or 4 (severe) on the EGSS at the Baseline visit. The following scores will be used to describe the severity grade and subsequent score:

Table 4. Evaluator's Global Severity Score – Face

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost Clear	Rare non-inflammatory lesions present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some non-inflammatory lesions are present, with few inflammatory lesions

		(papules/pustules only; no nodulocystic lesions)
3	Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be 1 nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to 2 nodulocystic lesions

For any subjects participating in the optional treatment of truncal acne (neck, upper chest, upper back and shoulders), Investigators will use the TSS scale below to grade truncal acne at each visit (starting at Baseline), recording the score as a separate score from the facial EGSS acne score on a separate TSS form.

Table 5. Truncal Severity Score (TSS) – Neck, Upper Chest, Upper Back & Shoulders

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost Clear	Rare non-inflammatory lesions present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be 1 nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to 2 nodulocystic lesions

11.2.2 Lesion Counts

The facial area lesion counts will be taken from the subject's face (including the nose). The lesion count groups will be inflammatory and non-inflammatory. Facial inflammatory lesions (pustules, papules, and nodules) will be counted as follows: pustules and papules will be counted and recorded together, not separately; nodular lesions will be counted and recorded separately. Non-inflammatory lesions (open and closed comedones) will be counted and recorded together. The lesion counts will be collected at each visit and/or upon discontinuation. Note: lesions counts will not be conducted for truncal acne subjects. The following are definitions of each lesion type counted:

Inflammatory lesions are defined as follows:

Papule: An erythematous, raised, palpable lesion less than 5 mm in diameter
Pustule: An erythematous, raised, likely palpable lesion containing white exudate or pus less than 5 mm
Nodule: A deep-seated, erythematous, firm lesion greater than 5 mm in diameter

Non-inflammatory lesions are defined as follows:

Open comedone (blackhead):	A widely dilated sebaceous follicle plugged with darkly pigmented sebum
Closed comedone (whitehead):	A small, closed sebaceous follicle distended with sebum, with a white appearance

11.2.3 Other Assessments

Photography

At select study centers, photographs of the face will be taken at Baseline and at Weeks 4, 8, and 12. Only subjects who provide written photographic consent for facial photographs will be included in photography. Note: photographs of truncal acne (if applicable) will not be conducted.

11.3 Evaluation of Safety

Safety assessments will be conducted at baseline and each subsequent study visit.

11.3.1 Cutaneous Safety Evaluations

Cutaneous safety will be evaluated through an assessment, conducted at the time of the study visit, of selected local signs (i.e., signs present at the study drug application site) that include the following: scaling, erythema, hypopigmentation, and hyperpigmentation. The evaluator will assess all cutaneous safety signs. For subjects treating (optional) truncal acne, cutaneous safety evaluations will also be conducted on this area throughout the course of the treatment/study, and recorded separately.

Cutaneous safety signs that result in the subject's requiring a concomitant therapy, interruption of treatment, or discontinuation from the study, will be reported as an AE.

Scaling:

0 – None	No scaling
1 – Mild	Barely perceptible, fine scales present on limited areas of the face
2 – Moderate	Fine scale generalized to all areas of the face
3 – Severe	Scaling and peeling of skin over all areas of the face

Erythema:

0 – None	No evidence of erythema present
1 – Mild	Slight pink coloration
2 – Moderate	Definite redness
3 – Severe	Marked erythema, bright red to dusky dark red in color

Hypopigmentation:

0 – None	No evidence
1 – Mild	Slight, barely perceptible
2 – Moderate	Definite, evident
3 – Severe	Marked, prominent

Hyperpigmentation:

0 – None No evidence
1 – Mild Slight, barely perceptible
2 – Moderate Definite, evident
3 – Severe Marked, prominent

11.3.2 Tolerability Evaluations

Tolerability will be evaluated through an assessment, at the time of the study visit, of selected local symptoms (i.e., symptoms present at the study drug application site) that include itching, burning, and stinging. The subject will self-assess all tolerability symptoms; the assessment will be based on an average over the period since the previous study visit.

For subjects treating (optional) truncal acne, tolerability evaluations will also be conducted on this area throughout the course of the treatment/study, and recorded separately.

Tolerability symptoms that result in the subject's requiring a concomitant therapy, interruption of treatment, or discontinuation from the study, will be reported as an AE.

Itching:
0 – None No itching
1- Mild Slight itching, not really bothersome
2 – Moderate Definite itching that is somewhat bothersome
3 – Severe Intense itching that may interrupt daily activities and/or sleep

Burning:
0 – None No burning
1 – Mild Slight burning sensation; not really bothersome
2 – Moderate Definite warm, burning sensation that is somewhat bothersome
3 – Severe Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Stinging:
0 – None No stinging
1 – Mild Slight stinging sensation, not really bothersome
2 – Moderate Definite stinging sensation that is somewhat bothersome
3 – Severe Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

11.3.3 Medical History and Abbreviated Physical Examination

A medical history will be taken at Screening, and confirmed and revised if needed, at Baseline. Medical histories having resolved 2 or more years before Baseline need not be collected unless considered relevant by the investigator.

An abbreviated physical examination including measurements of weight and vital signs (blood pressure, heart rate, respiration rate, and oral temperature) will be performed at Screening, Baseline and Week 12 (end of treatment/study); height will also be measured, but only at the

Screening visit. Any abnormal physical examination findings will be recorded and evaluated for AE reporting.

11.3.4 Laboratory Tests

Clinical laboratory analyses (CBC/Diff and serum chemistry) will be conducted on blood samples collected from subjects at Baseline and Week 12. All results will be reported, including results that are abnormal. Clinically significant results, in the opinion of the investigator, should be reported as AEs. If an AE should require laboratory testing, the results of the test must be obtained by the study center and filed in the subject's documentation.

For pre-menses females and FOCBP, a serum pregnancy test will be conducted at Baseline and Week 12.

11.3.5 Pregnancy Tests

All females who are pre-menses and FOCBP will undergo serum pregnancy testing at the Baseline and Week 12 study visits, and urine pregnancy testing at Screening, prior to randomization at Baseline, and at Weeks 2, 4, 8 and 12. The urine pregnancy tests will be supplied by the CRO/designee.

11.4 Adverse Events

11.4.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the study drug. AEs include any unfavorable and unintended illness, sign, symptom, clinically significant laboratory test abnormality, or disease temporally associated with the use of a medicinal product that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the study drug(s) under study. The collection of AEs will begin following the subject's completion of the consent process to participate in the study.

11.4.2 Documenting Adverse Experiences

It is the responsibility of the investigator to document all AEs that occur during the course of the study. The AEs should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject at each study visit. Each AE which appears to be independent of any prior event will be reported separately.

All AEs occurring after the subject signs the informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered study drug-related. All AEs, whether in response to a query, observed by the study center personnel, or reported spontaneously by the subject, will be recorded. Any AEs deemed related to treatment reported or observed at the final study/treatment visit will be followed until stabilization or resolution.

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Cutaneous safety and tolerability signs and symptoms that result in the subject's requiring a concomitant therapy, interruption of treatment, or discontinuation from the study will be reported as an AE. The following data will be collected on all AEs and recorded on the appropriate eCRF:

- Event description (diagnosis preferred, if unknown, record the signs/symptoms)
- Onset date and end date
- Maximum intensity (severity)
- Seriousness
- Action taken regarding study drug
- Corrective treatment, if given
- Outcome

In addition, the investigator's assessment of causality will be recorded.

Vital sign and laboratory abnormalities are to be recorded as AEs only if they are clinically significant (for example: are symptomatic, requiring corrective treatment, increased monitoring, leading to discontinuation or fulfilling a seriousness criterion).

11.4.3 Serious Adverse Events

All AEs will be assessed as either serious or nonserious. An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death.
- Is immediately life threatening, (the term "life threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires in patient hospitalization or prolongation of existing hospitalization (hospitalization for elective surgery for a baseline condition is not considered an AE).
- Results in persistent or significant disability/incapacity (permanent or substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the above listed outcomes; examples of such events include, but are not limited to, allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Note: A spontaneous abortion will be considered an SAE, and must be reported to the Sponsor within 24 hours of your awareness of the event as outlined under Section 11.4.6.

11.4.4 Assessment of Severity

The severity assigned to an AE should be determined by the maximum severity of the AE. The categories described below should be used to estimate the severity of AEs:

- Mild: Transient or mild discomfort which is easily tolerated; no limitation in activity; no medical intervention/therapy required.
- Moderate: Mild to moderate limitation in activity, but does not prevent usual activity; some assistance may be needed; no or minimal medical intervention/therapy required.
- Severe: Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible; may be incapacitating or life threatening.

11.4.5 Assessment of Causality

The investigator should assess the relationship of the AE, if any, to the study drug as either "Related" or "Not Related." The following should be taken into account when assessing AE/SAE causality:

- Related: There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.
- Not Related: There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists.

The following should be considered when assessing AE/SAE causality:

- Positive temporal relationship to study drug, such as if the study drug was withdrawn and the SAE resolved, or the event recurred after re-introduction
- If there is a reasonable possibility that the AE is associated with an underlying or concomitant illness
- Possible association with previous or concomitant therapy
- No temporal relationship to the study drug and/or a more likely alternative etiology exists.
- If the AE is directly related to study procedures or there is a lack of efficacy

11.4.6 Reporting of Serious Adverse Events

Adverse events classified as “serious” require expeditious handling and reporting to sponsor or designee within 24 hours of study center notification to comply with regulatory requirements.

All SAEs, whether related or unrelated to study drug, must be immediately reported to the medical monitor and CRO contact within 24 hours of the investigator’s awareness of the event. All SAEs must be reported via secure transmission and must be submitted on a written SAE report form signed by the investigator within 24 hours of the investigator’s awareness of the event. Contact details for SAE submission and method of secure submission are provided within the SAE form.

Investigators should not wait to receive additional information to fully document the event before notifying medical monitor and Sponsor of an SAE. If only limited information is initially available, follow-up reports are required. Additional relevant information such as hospital records and autopsy reports should be provided to the Sponsor as soon as they are available. Should the investigator become aware of an SAE (regardless of its relationship to study drug) that occurs within 30 days after stopping the study drug, the SAE must be reported in accordance with procedures specified in this protocol.

All deaths of subjects, regardless of cause, and which are known to the Investigator will be reported on the appropriate eCRF for up to 30 days after the administration of study drug, regardless of the Investigator's opinion regarding drug relationship. Documentation of the subject’s cause of death and a copy of the pseudonymized autopsy or pseudonymized hospital report will also be provided. The Medical Monitor and CRO contact must be notified within 24 hours of knowledge of the event by telephone and submission of an SAE form for all subject deaths. Written follow-up must be received by the IRB/IEC and competent authority within five (5) calendar days of initial notification as required by local regulations. If cause of death is not available within 24-hour reporting period, “death” must be reported as SAE term to meet timelines and the cause of death actively queried and submitted as a follow-up as soon as available.

The investigator should take all appropriate measures to ensure the safety of the subjects, notably he/she should follow a subject with an SAE until the event has resolved or the condition has stabilized. This may imply that follow-up will continue after the subject has left the study, and that additional investigations may be requested by the Sponsor. When a SAE persists at the end of the study, the investigator will conduct follow-up contacts with the subject until the investigator/Sponsor agree the event is satisfactorily resolved and/or stabilized. If at any time after 30 days after administration of study drug, the investigator becomes aware of an SAE which he/she feels is related to study drug or procedure, this must also be reported immediately (within 24 hours of knowledge of occurrence) by telephone and secure transmission to the medical monitor and Sponsor and/or Sponsor designee.

11.4.7 Expedited Serious Adverse Event Reports

Expedited SAE reports are those that are both unexpected based on the reference document (Investigator Brochure) and are related (i.e., the relationship cannot be ruled out) to the study drug. The Sponsor will notify regulatory authorities of these AEs and all participating study centers in writing for submission by the investigator to the IRB/IEC as required by local regulations.

Upon receiving such notices, the investigator must review and retain the notice with the Investigator Brochure and immediately submit a copy of this information to the responsible IRB/IEC according to local regulations. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

11.4.8 Pregnancy

All pre-menses females and FOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of contraceptive failure is minimized. Abstinence is allowed as a birth control method.

Before enrolling a pre-menses female or FOCBP in this clinical study, the investigator must review the following information about study participation:

- Informed consent requirements
- Contraceptives in current use

Following review of this information and appropriate subject counseling, the investigator or designee and the subject must sign the informed consent/assent before study enrollment.

During the study, all pre-menses females and FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to study enrollment, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study drug and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving study drug, the study drug must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the subject will be followed until the pregnancy comes to term. A Pregnancy Report Form will be submitted to the sponsor, initially and at the end of the pregnancy, which includes the outcome of the pregnancy and any complications occurring during the pregnancy or the delivery. If any SAEs are associated with the pregnancy, including spontaneous abortion/miscarriage, an SAE form must be filled out in addition to the Pregnancy Report Form and submitted as per section 11.4.6.

All confirmed pregnancies must be immediately reported to the medical monitor and CRO contact within 24 hours of the investigator’s awareness of the pregnancy. All confirmed

pregnancies are to be reported on a pregnancy form using the same reporting procedure for an SAE under Section 11.4.6.

12 Statistics

All statistical processing will be performed using SAS® version 9.4 or later unless otherwise stated. Statistical significance for superiority analyses will be based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less. Non-inferiority of IDP-126 Gel to Epiduo® Forte will be assessed with 95% confidence intervals.

The primary method of handling missing efficacy data will be based on estimation using the method of Markov Chain Monte Carlo (MCMC) imputation. Estimation will be done for each treatment group separately so that the pattern of missingness for one group does not influence the estimation of missing data for another group. Groups of complete datasets following the estimation will be concatenated to form analysis datasets for the analyses and subsequent imputation result inference with SAS PROC MIANALYZE. Descriptive statistics will also be derived from the multiply imputed datasets.

A statistical analysis plan, describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

Evaluations and Analyses

Inflammatory lesions and non-inflammatory lesions will be recorded for each subject at Baseline and at Weeks 2, 4, 8, and 12. The absolute and percent change from baseline of inflammatory lesions and non-inflammatory lesions will be derived for each subject at Weeks 2, 4, 8, and 12.

The EGSS will be recorded for each Subject. The EGSS will be dichotomized into “success” and “failure” at Week 2, 4, 8 and 12 with a subject considered a success for those visits if the EGSS is at least 2 grades less than baseline and are Clear or Almost Clear. The TSS will be recorded for applicable subjects with truncal acne, and will be summarized at Week 2, 4, 8, and 12, with the percentage of subjects achieving at least a 2-grade reduction from baseline included in the summary. The TSS will be dichotomized into “success” and “failure” at Week 2, 4, 8 and 12 with a subject considered a success for those visits if the TSS is at least 2 grades less than baseline.

Subjects will be asked to complete the Acne-Specific Quality of Life Questionnaire at Baseline and Week 12.

The two IDP-126 Vehicle Gel groups are combined for purposes of analyses.

12.1 Assessment of Efficacy

Primary, secondary and supportive efficacy analyses will be conducted on the ITT (primary) population. Primary efficacy analyses will be conducted on the PP (supportive) population.

12.1.1 Primary Efficacy

There are three co-primary efficacy endpoints:

- Absolute change from Baseline to Week 12 in inflammatory lesion counts
- Absolute change from Baseline to Week 12 in non-inflammatory lesion counts
- Percentage of subjects who achieve at least a two-grade reduction from Baseline and are "Clear" or "Almost Clear" at Week 12 in the EGSS.

12.1.2 Secondary Efficacy

The secondary efficacy endpoints will be the following:

- Absolute change in inflammatory and non-inflammatory lesion counts from Baseline at Weeks 2, 4, and 8
- Percent of subjects who achieve at least a 2-grade reduction from Baseline and are "Clear" or "Almost Clear" at Week 2, 4, and 8 in the EGSS
- Percent change in inflammatory and non-inflammatory lesion counts from Baseline at Weeks 2, 4, 8, and 12
- Percent of subjects who achieve at least a 2-grade reduction from Baseline at Week 2, 4, 8 and 12 in the TSS.

12.1.3 Non-Inferiority for Lesion Count Variables Evaluator's Global Severity Score

This section provides the basic model and statistical approach which is used in combination with the multiple imputation procedures described in Section 12.1.9. Non-inferiority of IDP-126 Gel to Epiduo® Forte will be assessed with 95% confidence intervals with the following non-inferiority margins:

- Absolute change from Baseline to Week 12 in inflammatory lesion counts: 2.1
- Absolute change from Baseline to Week 12 in non-inflammatory lesion counts: 2.1
- Percentage of subjects who achieve at least a two-grade reduction from baseline and are "Clear" or "Almost Clear" at Week 12 in the Evaluator's Global Severity Score: 10%

Confidence intervals of the difference in means (IDP-126 – Epiduo® Forte) for the absolute change from Baseline in inflammatory and non-inflammatory lesions will be based on based on an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate If the treatment-by-analysis center interaction effect is significant at an alpha less than 0.10, then the effect will be included in the model; otherwise it will be removed.

12.1.4 Test of Superiority for Lesion Count Variables Evaluator's Global Severity Score

This section provides the basic model and statistical approach which is used in combination with the multiple imputation procedures described in Section 12.1.9. Tests of superiority for the absolute change from Baseline in inflammatory and non-inflammatory lesions will be based on

based on an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate If the treatment-by-analysis center interaction effect is significant at an alpha less than 0.10, then the effect will be included in the model; otherwise it will be removed.

12.1.5 Statistical Hypothesis Testing and Control of Multiplicity

In order to control the Type I error rate, testing of primary endpoints will be performed sequentially, in the order listed below:

IDP-126 Gel vs IDP-126 Vehicle Gel

- Superiority for Dichotomized EGSS
- Superiority for Absolute Change in Inflammatory Lesion Counts
- Superiority for Absolute Change in Non-Inflammatory Lesion Counts

Epiduo® Forte vs IDP-126 Vehicle Gel

- Superiority for Dichotomized EGSS
- Superiority for Absolute Change in Inflammatory Lesion Counts
- Superiority for Absolute Change in Non-Inflammatory Lesion Counts

IDP-126 Gel vs Epiduo® Forte

- Non-Inferiority for Dichotomized EGSS
- Non-Inferiority for Absolute Change in Inflammatory Lesion Counts
- Non-Inferiority for Absolute Change in Non-Inflammatory Lesion Counts
- Superiority for Dichotomized EGSS
- Superiority for Absolute Change in Inflammatory Lesion Counts
- Superiority for Absolute Change in Non-Inflammatory Lesion Counts

If all primary endpoint comparisons are statistically significant, then testing will continue for the secondary endpoints in the following order, for IDP-126 Gel vs IDP-126 Vehicle Gel:

- Percent change in inflammatory lesion counts from Baseline at Week 12
- Percent change in non-inflammatory lesion counts from Baseline at Week 12
- Percent of subjects who achieve at least a 2-grade reduction from Baseline and are “Clear” or “Almost Clear” at Week 8 in the EGSS
- Absolute change in inflammatory lesion counts from Baseline at Week 8
- Absolute change in non-inflammatory lesion counts from Baseline at Week 8
- Percent change in inflammatory lesion counts from Baseline at Week 8
- Percent change in non-inflammatory lesion counts from Baseline at Week 8

- Percent of subjects who achieve at least a 2-grade reduction from Baseline and are "Clear" or "Almost Clear" at Week 4 in the EGSS
- Absolute change in inflammatory lesion counts from Baseline at Week 4
- Absolute change in non-inflammatory lesion counts from Baseline at Week 4
- Percent change in inflammatory lesion counts from Baseline at Week 4
- Percent change in non-inflammatory lesion counts from Baseline at Week 4
- Percent of subjects who achieve at least a 2-grade reduction from Baseline and are "Clear" or "Almost Clear" at Week 2 in the EGSS
- Absolute change in inflammatory lesion counts from Baseline at Week 2
- Absolute change in non-inflammatory lesion counts from Baseline at Week 2
- Percent change in inflammatory lesion counts from Baseline at Week 2
- Percent change in non-inflammatory lesion counts from Baseline at Week 2
- Percent of subjects who achieve at least a 2-grade reduction from Baseline at Week 12 in the TSS
- Percent of subjects who achieve at least a 2-grade reduction from Baseline at Week 8 in the TSS
- Percent of subjects who achieve at least a 2-grade reduction from Baseline at Week 4 in the TSS
- Percent of subjects who achieve at least a 2-grade reduction from Baseline at Week 2 in the TSS

12.1.6 Descriptive Statistics

Descriptive statistics will be presented for the following parameters by treatment group for both the ITT and PP analysis sets:

- Frequency and percent distributions of the EGSS at Baseline and Weeks 2, 4, 8, and 12.
- Frequency and percent distributions of the dichotomized (two-grade reduction from Baseline and are Clear or Almost Clear; two-grade reduction from Baseline) EGSS at Weeks 2, 4, 8, and 12.
- Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be used to summarize inflammatory and non-inflammatory lesion counts at Baseline and Weeks 2, 4, 8, and 12.
- Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be used to summarize the absolute and percent change in inflammatory and non-inflammatory lesion counts at Weeks 2, 4, 8, and 12.

12.1.7 Missing Efficacy Data Imputations

Lesion Count Variable Missing Data Imputation

Missing data will be estimated by multiple imputation and subsequently analyzed. Missing lesion count data will be derived for the analysis using the method of Markov Chain Monte Carlo (MCMC) multiple imputation. The pattern of missing observations in each treatment group will not influence the missing value estimation in the other because the imputation is being conducted independently for each treatment group.

Multiple imputation and subsequent analysis will involve 4 distinct phases with these principal tasks:

1. Create a data set of subjects, one for each treatment group, with observed values and those needing estimation by MCMC. The missing lesion count values in each data set will be filled in using the MCMC method 5 times to generate 5 data sets. The resulting data sets for each treatment arm will be combined into one complete data set for each imputation.

   Syntax:

```
proc mi data=datain out=dataout seed=&seed. nimpute=5 <options>;
  where trtpn=(1, 2, 3);
  mcmc chain=multiple;
  var baseline week2 week4 week8 week12;
run;
```

3. For each complete data set, the absolute change in lesion counts will be computed. Each complete data set will be analyzed as specified for the particular analysis.
4. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 6 random seeds will be needed to impute inflammatory lesion counts and non-inflammatory lesion counts for the five treatment groups. Those 6 random seeds have been pre-specified by using a random number generator:

- Inflammatory Lesion Counts; IDP-126 Gel: Seed=1228911621
- Inflammatory Lesion Counts; Epiduo® Forte Gel: Seed=1083128177
- Inflammatory Lesion Counts; IDP-126 Vehicle Gel: Seed=138767001
- Non-Inflammatory Lesion Counts; IDP-126 Gel: Seed=239363547
- Non-Inflammatory Lesion Counts; Epiduo® Forte Gel: Seed=1663970906
- Non-Inflammatory Lesion Counts; IDP-126 Vehicle Gel: Seed=1896067066

EGSS Missing Data Imputation

A similar procedure will be used for the analyses based on proportion of EGSS successes wherein the ANCOVA analysis is replaced with a logistic regression analysis. Specifically, missing EGSS values from which the dichotomized EGSS is derived will be estimated by MCMC. The pattern of missing observations in each treatment group will not influence the

missing value estimation in the other because the imputation is being conducted independently for each treatment group.

The missing EGSS values will be derived for the analysis using the method of Markov Chain Monte Carlo (MCMC) multiple imputation. Multiple imputation and subsequent analysis will involve 4 principal tasks:

2. Create a data set, one for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing EGSS values in each data set will be filled in using the MCMC method 5 times to generate 5 data sets. The resulting data sets for each treatment arm will be combined into one complete data set by imputation.

   Syntax:

   ```
   proc mi data=datain out=dataout seed=&seed. nimpute=5 <options>;
     where trtpn=(1, 2, 3);
     mcmc chain=multiple;
     var baseline week2 week4 week8 week12;
   run;
   ```

3. For each complete data set, the dichotomous success rate (clear or almost clear with a 2-point change from baseline) will be computed. The 12-week imputed EGSS values will be rounded to the nearest integer value prior to evaluating the success rate. Each complete data set will be analyzed with a logistic regression with factors of treatment group and analysis center.
4. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 3 random seeds will be needed to impute EGSS for the five treatment groups. Those 3 random seeds have been pre-specified by using a random number generator:

- EGSS; IDP-126 Gel: Seed=176867465
- EGSS; Epiduo® Forte Gel: Seed=1813154290
- EGSS; IDP-126 Vehicle Gel: Seed=2066562888

12.1.8 Subject Self-Assessments

Subjects will be asked to complete the Acne-Specific Quality of Life Questionnaire (Appendix 17.3). Descriptive statistics will be used to summarize the data reported for the questionnaire. No inferential analyses will be conducted.

12.2 Assessment of Safety

All safety assessments will be conducted using the safety analysis set.

Safety will be evaluated by tabulations of AEs, and Cutaneous Safety and Tolerability Evaluations. Cutaneous Safety Evaluation scores (erythema, scaling, hypo/hyper-pigmentation)

and Tolerability (itching, burning, and stinging) will be presented with descriptive statistics at Baseline and at Weeks 2, 4, 8, and 12 for each treatment group. In addition, the percent of subjects who experience a cutaneous reaction graded at a level of 3 at any point in the study following the first application of study drug will be tabulated. Frequencies and percentages for each outcome category will be included in these statistics. Mean values will be presented graphically by week and treatment group.

12.2.1 Adverse Events

All AEs occurring during the study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Descriptions of AEs will include the date of onset, the date the AE ended, the severity of the AE, the relationship to study drug, the action taken regarding study drug usage, the action taken to treat the AE, and the outcome.

Treatment-emergent adverse events (TEAEs) are those events with an onset on or after the date of the first study drug application. All reported TEAEs will be summarized by the number of subjects reporting TEAEs, system organ class, preferred term, severity, seriousness, and relationship to study drug.

Adverse events will be summarized by treatment group and severity. Each subject will be counted only once within a system organ class or a preferred term by using the AEs with the highest severity within each category.

Adverse events will be summarized by treatment group and relationship to study drug. Each subject will be counted only once within a system organ class or a preferred term by using the AEs with the greatest relationship within each category.

The percentage of subjects reporting AEs will be summarized by treatment group for AEs occurring in at least 5% of subjects (in any treatment group). The percentage of subjects for each treatment group will be compared using a Fisher's Exact test.

All information pertaining to AEs noted during the study will be listed by subject, detailing the verbatim term given by the investigator, preferred term, system organ class, start date, stop date, severity, action taken, and drug relatedness. The AE onset will also be shown relative (in number of days) to the day of initial dose of the randomized study drug.

Serious adverse events will be tabulated by subject within treatment groups.

In addition, a list of subjects who discontinued from the study and a list of subjects who experienced SAEs will also be provided.

12.2.2 Safety Laboratory Tests

Changes from baseline in safety laboratory values will be summarized with descriptive statistics at all applicable study visits. Shift tables will be presented for changes in safety laboratory values. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment time point will also be

provided. Determination of clinical significance for all out-of-range laboratory values will be made by each investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

12.2.3 Vital Sign Measurements

Changes from baseline in vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits. In addition, shifts in vital sign results (normal to abnormal, abnormal to normal, etc., based on the normal ranges) from Baseline to Week 12 (or ET) will be summarized using shift tables.

Individual vital sign test results will be presented in a by-subject listing. A listing of all out-of-range vital sign measurements at any assessment time point will also be provided.

12.2.4 Concomitant Medications

All recorded prior and concomitant medications will be classified based on terminology from the World Health Organization (WHO) Drug Dictionary. Therapies and medications data will be presented in data listings.

12.3 Subject Disposition

A tabulation of subject disposition will be provided. The tabulation will include the numbers of subjects who enter the study, complete the study, and discontinue the study. The reasons for discontinuation will be included.

12.4 Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized by study drug group using both the ITT, PP, and the Safety analysis sets. For continuous variables (eg, age), comparisons among the 3 study drug groups will be conducted using a two-way analysis of variance with factors of treatment and analysis center. Ethnicity and race will be analyzed with a Cochran-Mantel-Haenszel stratified by analysis center. Past and current medical conditions, as well as history of disease, will be presented in data listings and not be compared statistically.

12.5 Protocol Deviations

All protocol deviations will be reported to the Sponsor and recorded throughout the study. A tabulation of protocol deviations will be included in a data listing.

12.6 Compliance

The number and percentage of subjects who are compliant in each treatment group will be summarized descriptively. Subjects may not miss more than five consecutive days of dosing and must take 80-120% of expected doses to be considered compliant. The number of expected doses will be determined for each subject based on the length of their participation in the study and will

be capped at 89 days; the number of planned doses given a subject attended the Week 12 visit on the latest day within window.

12.7 Interim Analyses

No interim analyses are planned.

12.8 Additional Statistical Considerations

12.8.1 Analysis Sets

Approximately 660 subjects at least 12 years of age and older with moderate or severe acne (a score of 3 or 4 [moderate to severe] using the EGSS) will be enrolled and randomized in the study. With a 2:2:1:1 randomization ratio, it is anticipated that:

- 220 subjects to receive IDP-126 Gel, once daily application
- 220 subjects to receive Epiduo® Forte Gel, once daily application
- 110 subjects to receive IDP-126 Vehicle Gel (stored at 2-8°C), once daily application
- 110 subjects to receive IDP-126 Vehicle Gel (stored at CRT), once daily application

The ITT analysis set will consist of all randomized subjects who received study drug. The safety analysis set will be comprised of all randomized subjects who are confirmed to have dosed at least once.

An ITT analysis will be conducted, as well as a PP analysis. Subjects will be eligible for the PP analysis if they complete the 12-week evaluation without noteworthy study protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the study drug or the precise evaluation of study drug efficacy). The PP analysis set will include subjects in the safety analysis set who do not meet any of the following criteria:

- Failed any of the inclusion/exclusion criteria.
- Have taken any interfering concomitant medications.
- Did not attend the Week 12 visit.
- Missed more than 1 post baseline study visit prior to Week 12.
- Have not been compliant with the dosing regimen (i.e., subjects may not miss more than 5 consecutive days of dosing and must take 80%-120% of expected doses; the number of expected doses will be determined for each subject based on the length of their participation in the study).
- Out of visit window at the 12-week visit.

Subjects who discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect (and/or worsening of condition) will be included in the PP population. Prior to breaking the blind, other additional criteria may be added to the list to

accommodate for unforeseen events that occurred during the conduct of the study that result in noteworthy study protocol violations.

12.8.2 Sample Size Determination

Power calculations are based primarily on the Week 12 results of the Phase 2 study, V01-126A-201. This study was a five-arm study including IDP-126 Gel versus each of the dual components and Vehicle Gel. Furthermore, Component A (BPO 3.1%/adapalene 0.15%) is considered the component of IDP-126 which is analogous to Epiduo®, and Epiduo® indicated nearly identical reduction in non-inflammatory lesions to Epiduo® Forte Gel. Using estimates from the V01-126A-201 study for Component A and IDP-126 Vehicle Gel to define the non-inferiority margin and for power calculation assumptions allows for the use of estimates within one study thus avoiding comparisons between different studies which are under different timeframes and different conditions.

A total of approximately 660 randomized subjects are planned for this study, including 220 subjects each in the IDP-126 Gel and Epiduo® Forte Gel groups, and 110 subjects each in the IDP-126 Vehicle Gel groups, based on the results of the IDP-126A study as below.

V01-126A-201 Results				
		IDP-126	**IDP-126 Component A**	**IDP-126 Vehicle**
		(N=146)	(N=150)	(N=148)
Inflammatory Lesions	LSMean (SD)	29.9 (11.9)	26.7 (11.7)	19.6 (12.1)
Non-Inflammatory Lesions	LSMean (SD)	35.5 (16.3)	29.9 (16.4)	21.8 (16.6)
EGSS	Success (%)	52.5	27.8	8.1

A sample size of 220 for the IDP-126 group and 220 for the combined Vehicle Gel group has greater than 95% power to detect a statistically significant difference in Inflammatory Lesions, Non-Inflammatory Lesions, and in the percentage of subjects who have at least a 2 grade reduction at Week 12 from baseline in EGSS and were Clear or Almost Clear with a significance level of 0.05.

A sample size of 220 for the IDP-126 group and 220 for the Epiduo® Forte Gel group has greater than 95% power to detect non-inferiority of Inflammatory Lesions, Non-Inflammatory Lesions, and in the percentage of subjects who have at least a 2 grade reduction at Week 12 from baseline in EGSS and were Clear or Almost Clear with a significance level of 0.05.

A sample size of 220 for the IDP-126 group and 220 for the Epiduo® Forte Gel group has greater than 95% power to detect a statistically significant difference in the percentage of subjects who have at least a 2 grade reduction at Week 12 from baseline in EGSS and were Clear or Almost Clear with a significance level of 0.05. Additionally, this provides approximately 80% power to detect a statistically significant difference in Inflammatory Lesions and greater than 90% power to detect a statistically significant difference in Non-Inflammatory Lesions based on a two-sided t-test and a significance level of 0.05.

12.8.3 Handling of Missing Data

The method of multiple imputation will be used (see Missing Efficacy Data Imputations section).

12.8.4 Multicenter Issues

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational site. The study is intended to be conducted in a manner such that a minimum of 18 subjects will be enrolled for any investigator (i.e., approximately 6 subjects in each of the IDP-126 Gel and Epiduo® Forte arms and 3 subjects in each IDP-126 Vehicle Gel arm). In the event that there are too few subjects for an investigator, then this investigator's data will be combined, within geographic region to achieve the desired sample size minimum per arm. The combining of investigator's data will be accomplished by taking the investigator with the smallest enrollment and combining it with the investigator with the largest enrollment. If there is a further need to combine data, then the data of the investigator with the second smallest enrollment will be combined with the investigator's data which had the second largest enrollment, and so on. This process will continue for all investigators who did not have a minimum of 18 subjects. The process of combining investigator data that have insufficient subjects per treatment arm will result in redefining the groups of investigators for the purposes of statistical analyses. These combined groups will be referred to as "analysis centers" in the statistical analyses based on ANCOVA and stratified logistic testing.

Prior to investigating the treatment effect within the analysis centers, the magnitude of the site main effect will be investigated to determine if the main site-to-site variability is such that it could mask the analysis center effects. Thus, prior to pooling, the lesion count data at Week 12 will be analyzed with an ANCOVA with factors of treatment group, site, and the interaction term of treatment group by site and also the percent of subjects with treatment success at Week 12 will be analyzed with a logistic regression with factors of treatment group, site, and the interaction term of treatment group by site. If theses analyses are not computationally feasible due to some sites having very few subjects enrolled, the low enrolling sites will be excluded from these analyses.

The consistency of treatment response will be investigated across the analysis centers subsequent to combining the data as described above. Statistical tests will be conducted to identify if there

are extreme analysis centers that could affect the interpretation of common statistical and clinical conclusions. An analysis center by treatment interaction will be included in the primary variable analyses to test for parallel treatment effect at an alpha level of 0.10. Change from baseline in inflammatory lesions and non-inflammatory lesions will be analyzed with an ANCOVA with factors of treatment, analysis center, and treatment by analysis center interaction and the respective baseline lesion count variable as a covariate. For the purpose of testing consistency of treatment response, the dichotomized EGSS will be analyzed with a logistic regression procedure with factors of treatment, analysis center, and treatment by analysis center interaction. Further examination will follow for any variables that have a significant ANCOVA or logistic regression interaction term. In the event that the ANCOVA or logistic regression interaction (referred to henceforth as the "appropriate test") p-value is less than or equal to 0.10, a sensitivity analysis that excludes analysis centers with the extreme efficacy result will be performed to determine the robustness of the treatment effect. On the other hand, if the outcome of the appropriate test has a p-value greater than 0.10, then the conclusions from the pooled data will be considered to be free of the impact of extreme analysis centers.

The first step in conducting a sensitivity analysis is to identify the extreme analysis center or centers that contribute to the statistical significance of the appropriate test. The process involves submitting subsets of analysis centers to the appropriate test and observing the appropriate test p-value for the subset. Subsets with p-values greater than 0.10 for the appropriate test are considered homogeneous.

The search for an extreme analysis center begins by analyzing all subsets that can be created by excluding one analysis center. If one or more of the subsets result in an appropriate test p-value greater than or equal to 0.10, then the analysis center excluded from the subset with the largest p-value for the appropriate test is deemed to be the extreme analysis center.

If all appropriate test subset p-values are less than or equal to 0.10, then the process will analyze the appropriate test for all subsets that can be created by excluding two analysis centers. If one or more of these subsets generate appropriate test p-values larger than 0.10, then the analysis centers excluded from the subset with the largest appropriate test p-value are deemed the extreme analysis centers.

Thus, the process of identifying the extreme analysis centers will continue in a stepwise manner by first excluding one, then two, then three, etc., analysis centers until the appropriate test p-value exceeds 0.10.

Once the extreme analysis center or centers have been identified, then the treatment p-values of the remaining analysis centers will be computed. Inferences will be drawn from the treatment p-value, as well as any pertinent observations regarding the extreme analysis center or centers. Additionally, it is noted that this process excludes subjects from the analysis in a non-random manner and has an unpredictable impact on the power of the treatment effect test. In the event that the treatment effect of the remaining subset is not statistically significant, due consideration

of the post-hoc aspects of the process will be given when the results are interpreted. Conclusions will be presented by the sponsor as appropriate to the findings of the sensitivity analysis.

12.8.5 Multiplicity Issues

The overall Type I error will be controlled. See Section 12.1.6 for further detail about control of Type I error across primary endpoints.

12.8.6 Windowing Rules

The timing of all study visits is relative to Baseline (Day 0). The Week 2, Week 4, and Week 8 visits should occur within ± 3 days of the scheduled times, the Week 12 visit should occur within −3/+5 days of the scheduled time.

13 Quality Control and Quality Assurance

13.1 Study Monitoring

An Investigator Meeting and/or an initiation visit will be conducted with the principal investigator and study coordinators by the sponsor and/or its designee. During this meeting, an extensive review and discussion of the protocol, the roles of the study staff, all study procedures, source documents, and eCRFs will be conducted. Evaluation scales will be reviewed extensively, and documentation of training will be recorded for training of Sponsor-approved evaluators.

The study monitors/clinical research associates will be trained prior to study initiation. Following this training, an overview of the study disease and study material background will be understood. Specific monitoring guidelines and procedures to be followed during monitoring visits will also be presented. During the course of the study, all data will be 100% source document-verified by the monitors when possible. All subject source documents must be made available to the monitors.

The conduct of the study will be closely monitored by the sponsor following GCP guidelines. The reports of these verifications will also be archived with the study report. In addition, inspections or on-site audits may be carried out by local authorities or by the Sponsor's Quality Assurance Department. The investigators will allow the Sponsor's representatives and any regulatory agency to examine all study records, corresponding subject medical records, clinical dispensing records and storage area, and any other documents considered source documentation. The investigators agree to assist the representative, if required.

13.2 Audits and Inspections

The study will be conducted under the sponsorship of Bausch Health in conformance with all appropriate local and federal regulations, as well as ICH guidelines. Interim and end of study audits of raw data, study files, and the final report may be conducted by Bausch Health's Quality Assurance Department or designee.

The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. In addition, the sponsor will be responsible for securing agreement from all involved parties to ensure direct access to all study related study centers, source data/documents, eCRFs, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities.

13.3 Data Quality Assurance

All assessments performed will be accurately documented in the subject's source documents and eCRFs. The investigator or designee will enter the information required by the protocol into the source documents and eCRFs provided by the sponsor or designee. Subjects will be identified in the eCRFs by their assigned subject number only.

The investigators must read the protocol thoroughly and must follow the instructions exactly. Any deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate written protocol amendments made prior to implementing the agreed changes. Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without written approval from the Sponsor.

14 Ethics and Administrative Issues

14.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP, and in compliance with local regulatory requirements. The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

14.2 Ethics Review and Competent Authority Approval

This protocol, proposed informed consent/assent form, other information to subjects, and all appropriate protocol amendments will be properly reviewed and approved by an IRB or IEC and the competent authority as required. Documentation of all required approvals must be available prior to initiation of the study. The investigator must ensure that IRB or IEC and competent authority approvals are in place as required before implementation of protocol amendments or amendments to any other study documents. The name and occupation of the chairman and members of the IRB/IEC will be supplied to the Sponsor. The investigator will provide required progress reports and report all SAEs to the IRB/IEC as required by the IRB/IEC.

14.3 Written Informed Consent/Assent

Written informed consent/assent, in accordance with local clinical investigation regulations, must be obtained prior to participation in the study. Subjects less than age of consent must sign an assent for the study and a parent or a legal guardian must sign the informed consent (if subject reaches age of consent during the study they should be re-consented at the next study visit). The investigator or designee will discuss the purpose of the study with each subject, and provide a description of the study drug (including any potential and possible side effects) and the study procedures. Information must be given both in oral and written forms. Subject information will be provided in a language understandable to the subject and may not include any language that appears to waive any of the subject's legal rights or appears to release the investigator, the Sponsor, or the institution from liability or negligence.

The investigator will provide the prospective subject sufficient time to consider whether or not to participate, minimizing the possibility of coercion or undue influence and will discuss any questions the subject may have. The investigator will explain to the subject that participation in the study is voluntary and that withdrawal from the study is possible at any time without detriment to care. The consent must include acknowledgment that medical records and medical data derived from the study may be forwarded to the Sponsor or to responsible local or federal authorities.

No subject can enter the study or have any study related procedures performed before his/her written informed consent/assent has been obtained. The original signed and dated informed consent/assent form will be retained with the study records, and a copy of the signed form will be given to the subject.

An informed consent/assent template will be supplied by the sponsor or designee. Any changes to the informed consent/assent form must be agreed to by the sponsor or designee. Only consent/assent forms approved by the IRB/IEC and competent authority, as applicable, must be used.

14.4 Subject Data Protection

Subject data will be protected by ensuring that no captured data contain subject names, addresses, telephone numbers, email addresses, or other direct personally identifying information. Subject data recorded on eCRFs during the study will be documented in a coded fashion. The subject will only be identified by the subject number and year of birth. Confidentiality of subject records will be maintained to ensure adherence to applicable local privacy regulations. Other than where necessary to meet regulatory requirements, all data collected in this study will be presented in tabulated (i.e., aggregate) form and listings containing information that could be used to identify an individual subject will not be included in any public disclosures of the study data or the study results.

14.5 Data Monitoring Committee

Not applicable.

14.6 Financial Disclosure

Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest. An original Financial Disclosure Form (FDF) must be completed, signed and dated by the principal investigator (PI) and any sub-investigators and study staff performing significant tasks in the study. All FDFs will be collected by the Sponsor or its designee and filed in the study Trial Master File. A copy of all FDFs will be retained in the Investigator Site Binder.

14.7 Finance

The study is financed by the Sponsor.

14.8 Investigator Obligations

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

14.9 Changes to the Protocol

The investigators must read the protocol thoroughly and must follow the instructions exactly. Whenever possible, any planned deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate documentation of sponsor approval prior to effecting the changes agreed upon. Any amendment to the protocol containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB/IEC and competent authority, as applicable before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

14.10 Confidentiality/Publication of the Study

All the data furnished to the investigator and his/her staff and all data obtained through this protocol will be regarded as confidential and proprietary in nature and will not be disclosed to any third party, except for the FDA or other regulatory body, without written consent from the sponsor.

15 Data Handling and Record Keeping

15.1 Inspection of Records

Investigators must maintain detailed records on all study subjects who are enrolled in the study or undergo screening. Data will be recorded in the subject's source documents and in applicable study logs provided by the Sponsor. Source documents include subject medical records, hospital charts, clinic charts, investigator subject study files, as well as the results of diagnostic tests (eg, laboratory tests). All required data should be recorded in the study documentation completely for prompt data review. Upon study completion or at any other time specified by the sponsor or designee, the appropriate study documents must be submitted.

The investigator must keep accurate separate records (source documentation) of all subject visits, being sure to include all pertinent study related information. At a minimum, this includes the following information:

- A statement indicating that the subject has been enrolled in the study and the subject number
- Date that informed consent/assent was obtained
- Evidence that the subject meets study eligibility requirements (eg, medical history, screening evaluations)
- Dates of all study related visits and results of any evaluations/procedures performed, including who performed each assessment at each visit
- Use of any concurrent medications during the study
- Documentation of study drug accountability
- Any and all side effects and AEs must be thoroughly documented to conclusion
- Results of any diagnostic tests conducted during the study
- The date the subject exited the study and a statement indicating that the subject completed the study or was discontinued early, including the reason for discontinuation

Notes describing telephone conversations and all electronic mail with the subject or the sponsor (sponsor's designee) concerning the study must be recorded or kept on file. All source documents must be made available to the sponsor and the sponsor's designated monitor upon request.

15.2 Retention of Records

The investigator should properly store and maintain all study records in accordance with sponsor directives. All records relating to the conduct of this study are to be retained by the investigator until notified by the sponsor in writing that the records may be destroyed.

The investigator will allow representatives of the sponsor's monitoring team, the governing IRB/IEC, the FDA, and other applicable regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's clinic and/or hospital medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness and accuracy of the data being entered onto the eCRF, and compliance with FDA or other regulatory agency regulations.

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17 Appendices

17.1 Subject Instruction Sheet

These instructions are for the subject and/or the parent/legal guardian. The parent/legal guardian should help and monitor study drug application. Study drug should be applied **once daily** at about the same time each day approximately 30 minutes prior to bed time. Record the applications in the subject diary provided.

Study Materials:
The study drug is provided in a white pump.

First time use of the pump:

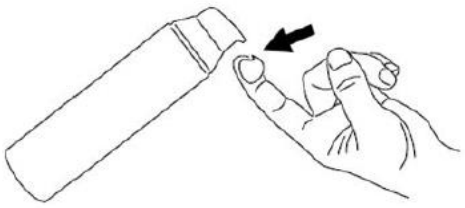
- Prior to first time use, the pump will have to be primed. Remove the cap of the study drug pump and fully depress the pump head
- During priming the product may not immediately come out evenly, or at all, when first pressing on the pump head. This is normal.
- To prime, continue to fully depress the pump head until product comes out evenly from the pump nozzle. Product that has come out during priming will be discarded.
- Priming will be performed during scheduled on-site clinic study visits where new pumps will be dispensed under the supervision of the clinic

<u>FOR ALL SUBJECTS APPLYING THE STUDY DRUG TO THE FACE:</u>

Wash your face gently with a mild cleanser approved by your study doctor and warm (not hot) water. Rinse thoroughly and gently pat dry with a cotton towel. Wait until skin is completely dry before applying the study drug.

A thin layer of study drug should be applied once daily in the evening, at least 30 minutes prior to bed time (about the same time every day) to the entire face for twelve weeks. Use the pump to dispense one pea-sized amount of study drug onto your fingertip (Figure 1). One pea-sized amount of study drug should be enough to cover your entire face.

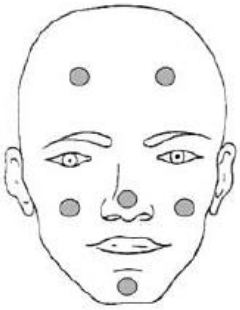
Figure 1



This dose should then be dotted on to 6 areas (chin, left cheek, right cheek, nose, left forehead, right forehead) on the face (Figure 2). After distributing the dose in this manner, gently rub the

gel into the skin. This amount should be used to evenly cover the entire face excluding the mouth, eyes and lips. It is important to treat your entire face.

Figure 2



Do NOT treat only specific lesions. DO NOT APPLY MORE THAN THE PRESCRIBED AMOUNT. Do NOT share your study drug with anybody, study drug is for your use only and will be weighed during your study visits to review the amount of study drug you have used.

Be sure to wash your hands after you apply the product.

FOR THE SUBSET OF SUBJECTS APPLYING STUDY DRUG TO THE TRUNK:

Wash the treatment area gently with a mild cleanser approved by your study doctor and warm (not hot) water. Rinse thoroughly and gently pat dry with a cotton towel. Wait until skin is completely dry before applying the study drug.

A thin layer of study drug should be applied once daily in the evening, at least 30 minutes prior to bed time (about the same time every day) to the entire treatment area (neck, upper chest, upper back and shoulders) for twelve weeks. It is recommended that white linen, white towels and white clothing is utilized for subjects applying the study drug to the trunk area to avoid bleaching.

You should continue to use the pump to dispense one pea size amount onto the fingertip. The study drug should be spread in a thin layer across the truncal area (neck, upper chest, upper back and shoulders). It is important that the study drug is spread evenly, and specific lesions are not treated. The study drug should become invisible almost immediately following application with gentle rubbing. Ensure to wash your hands after applying the study drug to the trunk and to place the cap back onto the pump after each use.

Reminders:

- On study visit days, study drug will be applied at your study center during the visit. On the day of the visit, do not apply study drug prior to your study visit or in the evening after your study visit.

- Avoid contact with the eyes, inside the nose, mouth and all mucous membranes. Caution: This product contains benzoyl peroxide which can bleach hair or colored fabric.
- Do not cover the affected areas with any type of dressing, such as gauze.
- THE STUDY DRUG SHOULD BE USED ONLY BY THE PERSON FOR WHOM IT WAS PRESCRIBED and it should be kept out of the reach of children or others of limited capacity to read or understand.
- Store this at room temperature up to 25°C (77°F). Do not freeze. Avoid excessive heat or cold.
- Containers of study drug must be returned to the study facility, even if they are empty.
- If you miss any doses, at your next visit inform the study doctor of the date(s) of the missed dose(s).
- Continue to use the same, study doctor approved, cleanser, moisturizer and sunscreen throughout the study.
- You must not use any other treatment for your facial acne while you are participating in this study.
- Avoid unnecessary sun exposure and tanning booths.
- It is recommended that white linen, white towels, and white clothing is utilized for subjects applying the study drug to the trunk area to avoid bleaching.

It is important that you inform the study center about any medications (i.e., prescriptions, over-the-counter medications, street drugs, or herbal medications) that you have taken during the study.

If you experience significant diarrhea while participating in the study contact the Study Doctor immediately.

If you have any questions or have a potential research-related side effect or injury you may contact _____ at _____.

Your study drug use by date is: _____ (DD/MMM/YYYY).

17.2 Cleansers, Moisturizers and Sunscreen Use Guidelines

Subjects may use the following products as examples of approved products. The Investigator may use their discretion on what products each subject may use in the treatment area during the study. Subjects may use the below set of examples or other Investigator approved non-medicated products on the treatment area. Information regarding products used should be captured in the source document and recorded on the facial skin care section of the eCRF.

Approved Cleanser Examples:

- CeraVe cleanser
- Cetaphil daily cleaner and gentle cleansing bar
- Purpose gentle cleansing wash

Approved Moisturizer Examples:

- CeraVe Cream or Lotion
- Moisturel cream or lotion
- Nutraderm
- Cetaphil lotion or cream
- DML
- Eucerin lotion or cream
- Purpose

Approved Moisturizer/Sunscreen Combination Product Examples:

- CeraVe Lotion AM
- Olay Complete (SPF 15)
- Neutrogena Health Defense Daily Moisturizer (SPF 30)
- Cetaphil Daily Facial Moisturizer (SPF 15)

Approved Sunscreen Examples:

- Banana Boat Sport Sunblock Lotion (SPF 15, 30+ or 50)
- Neutrogena UVA/UVB (SPF 30 or 45)
- Neutrogena Sensitive Skin Sunblock Lotion (SPF 17)
- Neutrogena Healthy Defense Oil-Free Sunblock Lotion (SPF 30 or 45)
- Coppertone Water Babies UVA/UVB Sunblock Lotion (SPF 45)

[redacted]