CLINICAL STUDY PROTOCOL

IDP-120

Protocol V01-120A-302

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2 Arm, Parallel Group Study Comparing the Safety and Efficacy of IDP-120 Gel and IDP-120 Vehicle Gel in the Treatment of Acne Vulgaris

Development Phase:	3
Study Design:	Multi-center, randomized, double-blind, vehicle-controlled efficacy and safety study
Date:	29 August 2019 (Amendment 2) 26 March 2019 (Amendment 1) 30 August 2018 (Original)
Sponsor:	Dow Pharmaceutical Sciences, a Division of Valeant Pharmaceuticals North America, LLC 1330 Redwood Way, Suite C Petaluma, CA 94954 707-793-2600

VALEANT
Research & Development

Protocol Review and Approvals

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2 Arm, Parallel Group Study Comparing the Safety and Efficacy of IDP-120 Gel and IDP-120 Vehicle Gel in the Treatment of Acne Vulgaris

Personnel Responsible for Conducting the Study

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2 Arm, Parallel Group Study Comparing the Safety and Efficacy of IDP-120 Gel and IDP-120 Vehicle Gel in the Treatment of Acne Vulgaris

Contract Research Organization / Medical Monitor

[redacted]

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Principal Investigator Protocol Agreement Page

I agree:

- To assume responsibility for the proper conduct of this clinical study at this site 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 (e.g., 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 investigational products(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, investigational product(s), and their clinical study-related duties and functions.

_____

Principal Investigator (print name)

_____ _____

Principal Investigator (signature) Date

2 Synopsis

Name of Sponsor/Company: Dow Pharmaceutical Sciences**,** a division of Valeant Pharmaceuticals North America, LLC
Name of Investigational Product: IDP-120 Gel
Name of Active Ingredients: tretinoin and benzoyl peroxide [BPO] gel, 0.05%/2.5%
Title of Study: A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2 Arm, Parallel Group Study Comparing the Safety and Efficacy of IDP-120 Gel and IDP-120 Vehicle Gel in the Treatment of Acne Vulgaris
Number of clinical centers: Multicenter, approximately 24-35 investigational centers in North America and Latin America
Objective: The primary objective of this study is to compare the safety, efficacy and tolerability of IDP-120 Gel and IDP-120 Vehicle Gel in the treatment of subjects with moderate to severe acne vulgaris.
Methodology: This is a multi-center, randomized, double-blind, vehicle-controlled, 12-week study designed to assess the safety, tolerability, and efficacy of IDP-120 Gel and IDP-120 Vehicle Gel at Weeks 2, 4, 8, and 12. To be eligible for the study subjects must be at least 9 years of age and have a clinical diagnosis of moderate to severe acne (defined as an EGSS score of 3 or 4), presenting with 20-50 inflammatory facial lesions (papules, pustules, and nodules), 25-100 non-inflammatory facial lesions (open and closed comedones), and $\leq$ 2 facial nodules. Approximately 600 subjects will be randomized to the following treatment groups: • 300 Subjects to IDP-120 Gel, once-daily application • 300 Subjects to IDP-120 Vehicle Gel, once-daily application 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. Study drug will be dispensed to the Subjects at Baseline, Week 4 and Week 8. 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 investigational center (with the exception of study visit days, where study drug will be applied by the subject on-site during the study visit). The investigator will assess the subject's face at each study visit. Information on reported and observed AEs will be obtained at each visit. An abbreviated physical exam and vital signs measurement will be performed at Baseline and Week 12 (Final Visit) visits for all subjects. Blood samples will be collected from subjects at Baseline and Week 12, for CBC/Diff, serum chemistry, and serum pregnancy (for pre-menses females and females of childbearing potential). For all pre-menses females and females of childbearing potential (FOCBP), urine pregnancy testing will be performed at Screening, Baseline prior to randomization, and at Weeks 2, 4, 8, and 12. All subjects will also be asked to complete the Acne-Specific Quality of Life Questionnaire at Baseline and Week 12. In addition, at selected sites, standardized photography of the face will be performed at Baseline and Weeks 2, 4, 8 and 12.
Number of subjects planned: Approximately 600 subjects with moderate to severe acne vulgaris will be enrolled and randomized in the study. Subject will be randomized to the following treatment groups: • 300 Subjects to IDP-120 Gel, once-daily application • 300 Subjects to IDP-120 Vehicle Gel, once-daily application

Inclusion criteria:

1. Male or female at least 9 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 a score of 3 (moderate) or 4 (severe) on the Evaluator's Global Severity assessment at the baseline visit;
4. Subjects with facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 20 but no more than 50;
5. Subjects with facial acne non-inflammatory lesion (open and closed comedones) count no less than 25 but no more than 100;
6. Subjects with two or fewer facial nodules;
7. Females of childbearing potential and females who are pre-menses must be willing to practice effective contraception for the duration of the study. (Effective contraception is defined as stabilized on oral contraceptive for at least 3 months, IUD, condom with spermicidal, diaphragm with spermicidal, implant, Nuvaring, injection, transdermal patch, abstinence or sterile partner.) Females on hormonal contraceptive must have taken the same type for at least three months prior to entering the study and must not change type during the study. Those who have used any hormonal contraception in the past must have discontinued usage at least three months prior to the start of the study. Women who use birth control for acne control only should be excluded.
8. Pre-menses females and females of childbearing potential must have a negative urine pregnancy test at the screening and baseline visits;
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).

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 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, make-up, soap, masks, washes, sunscreens, etc) to their face;
8. Female subjects who are pregnant, nursing mothers, planning a pregnancy during the course of the trial, or become pregnant during the study;
9. Use of hormones (eg, Depogen, Depo-Testadiol, Gynogen, Valergen, etc) for less than 12 weeks immediately preceding study entry; Subjects treated with hormones 12 or more consecutive weeks immediately prior to study entry need not be excluded unless the subject expects to change dose, drug or discontinue hormone use during the study;
10. If female, subject has a history of hirsutism, polycystic ovarian disease or clinically significant menstrual irregularities;

11. 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;
12. 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 mid-to super-high potency corticosteroids, phenytoin and phenobarbital); Multivitamins, including Vitamin A at recommended daily doses and Vitamin D at stable doses, are acceptable;
13. 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 tretinoin and benzoyl peroxide;
14. Concomitant use of potentially irritating over-the-counter products that contain ingredients such as benzoyl peroxide, alpha-hydroxy acid, salicylic acid, retinol or glycolic acids;
15. Subjects who have not undergone the specified washout period(s) for the following topical preparations or 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 (including comedone removal strips) 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 (e.g., BPO, salicylic acid)	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
- Facial procedures, including chemical peel, microdermabrasion, light (PDT, LED) and laser therapy, and acne surgery	4 weeks

If the subject requires topical treatment for acne on areas other than the face (e.g., chest and/or back), the investigator may prescribe a product that does not contain tretinoin or BPO, and must be noted in source documents and eCRF;

16. 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
- Antiobiotics	4 weeks
- Other systemic acne treatments	4 weeks
- Systemic retinoids	6 months

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

Investigational product, dosage and mode of administration:

Investigational Product: IDP-120 (tretinoin and benzoyl peroxide [BPO], 0.05%/2.5%) Gel, applied topically to the face, once daily for 12 weeks.

Comparator Product: IDP-120 Vehicle Gel, 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:

See comparator product above.

Criteria for evaluation:

Co-Primary efficacy:

IDP-120 Gel will be compared to IDP-120 Vehicle Gel.

Co-primary endpoints are:

(1) Superiority in absolute change from Baseline to Week 12 in mean inflammatory lesion counts
(2) Superiority in absolute change from Baseline to Week 12 in mean non-inflammatory lesion counts, and,
(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:

- Percent change in non-inflammatory lesion count from Baseline to Week 12
- Percent change in inflammatory lesion count from Baseline to Week 12
- Percentage of subjects who have at least a 2 grade reduction at Week 12 from Baseline in the Evaluator's Global Severity Score
- Percent change in non-inflammatory lesion count from Baseline to Week 8
- Percent change in inflammatory lesion count from Baseline to Week 8
- Percent change in non-inflammatory lesion count from Baseline to Week 4
- Percent change in inflammatory lesion count from Baseline to Week 4

Supportive Efficacy:

- Percent change in non-inflammatory lesion count from Baseline to Week 2
- Percent change in inflammatory lesion count from Baseline to Week 2
- Percentage of subjects who have at least a 2 grade reduction at Week 8 from Baseline in the Evaluator's Global Severity Score
- Percentage of subjects who have at least a 2 grade reduction at Week 4 from Baseline in the Evaluator's Global Severity Score
- Percentage of subjects who have at least a 2 grade reduction at Week 2 from Baseline in the Evaluator's Global Severity Score

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 two 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.

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. Evaluations 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.

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 nodulo-cystic 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 one nodulo-cystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to 2 nodulo-cystic lesions

Safety Assessments:

Cutaneous safety and tolerability will be evaluated by tabulations of adverse events and Cutaneous Safety and Tolerability Evaluation scores (scaling, erythema, hypo/hyperpigmentation, 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.

At selected sites, standardized photography of the face will be performed.

Statistical methods:

All statistical processing will be performed using SAS® version 9.3 or later unless otherwise stated. Statistical significance will be based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less. Tests of lesion count superiority will be based on an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate or on ranked data submitted to an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate. The co-primary analysis of the dichotomized EGSS will be based on logistic regression with factors of treatment group and analysis center. The primary method of handling missing efficacy data will be based on estimation using the method of Markov Chain Monte Carlo (MCMC) imputation. Additionally, a model-based multiple imputation process will be used as a sensitivity analysis to the MCMC imputation. The absolute change in lesion count will also be analyzed using a repeated measures ANCOVA for lesion count data or repeated measures logistic regression model (generalized estimating equations) for the dichotomized EGSS. Finally, a tipping point analysis will be performed for the primary endpoints.

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 were dispensed study drug.

The safety population will be comprised of all randomized subjects who are confirmed to have used the study drug at least once. 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 safety 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;
- 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 five consecutive days of dosing and must take 80-120% of expected doses. The number of expected doses will be determined for each subjects 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 trial that result in noteworthy study protocol violations.

Approximately 600 subjects with moderate or severe acne will be enrolled and randomized to the following treatment groups:

- 300 subjects to receive IDP-120 Gel, once-daily application
- 300 subjects to receive IDP-120 Vehicle Gel, once-daily application

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 and supportive 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 percent change in inflammatory and non-inflammatory lesion counts from baseline to Weeks 12, 8 and 4 and also percentage of subjects with at least a two grade improvement in the Evaluator's Global Severity Score from baseline to Week 12.

Supportive:

Additional supportive efficacy endpoints include percent change in inflammatory and non-inflammatory lesions counts from Baseline at Week 2, as well as percentage of subjects with at least a two grade improvement in the Evaluator's Global Severity Score from baseline at Weeks 2, 4, and 8.

Safety Evaluation:

All subjects who are confirmed to have used the study drug at least once will constitute the safety population. Safety will be evaluated by tabulations of adverse events (AEs), Cutaneous Tolerability Evaluations, vital signs/abbreviated physical exams, and safety labs.

Cutaneous Safety Evaluation scores (erythema, scaling, and 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. 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 signs, an abbreviated physical exam, and safety labs will be conducted on all subjects at specified visits. For pre-menses females and females of child-bearing potential (FOCBP), urine pregnancy testing 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 collected at Baseline and Week 12 Visits. 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 recorded prior and concomitant medications will be classified based on terminology from the WHO Drug Dictionary. Therapies and medications data will be presented in the data listings.

All adverse events occurring during the study will be recorded and classified on the basis of 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 regarding 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 adverse events 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 adverse events 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 any treatment group.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim 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-Assessment

Subjects will be asked to complete the Acne-Specific Quality of Life Questionnaire during the study. 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 GCP including the archiving of essential study documents. This protocol follows guidelines outlined by the International Conference on Harmonization (ICH). All data furnished to the investigator and his/her staff, and all data obtained through this stud, 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
ANCOVA	Analysis of Covariance
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EGSS	Evaluator's Global Severity Score
ET	Early termination
FDA	United States Food and Drug Administration
FOCBP	Female of Childbearing Potential
g	Gram
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LED	Light Emitting Diode
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Affairs
mL	Milliliter
OTC	Over-the-counter
PDT	Photodynamic Therapy
PP	Per protocol
QoL	Quality of Life
SAE	Serious adverse event
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. 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 usually begins at the time of the sharp increase in androgen production occurring in adolescence [1]. The disease is most prevalent amongst teenagers, but it does occur later in life, particularly in the third and fourth decade. The pathogenesis is complex and involves an androgen-stimulated increase in sebum production, associated with follicular hyperkeratinization and obstruction of the sebaceous follicles. This results in abnormal desquamation of the follicular epithelium, and is associated with bacterial proliferation (especially *Propionibacterium acnes (P. acnes)*) and chronic inflammation associated with acne. These changes in acne subjects result in enlarged sebaceous glands; obstruction of the follicular canal with associated sebum retention and distention of the follicle by tightly packed horny cells that lead to the formation clinical inflammatory lesions including superficial pustules such as comedones (popularly known as "blackheads" or "whiteheads"); and more deeply located papules, nodules and cysts [1]. The areas most affected by the disease include the pilosebaceous follicles of the head and upper trunk, where the sebaceous glands are particularly active [2].

Currently, therapeutic treatment of acne is directed against 3 principal pathogenic factors of the disease, including the bacterial colonization of follicles, the hypersecretion of the sebaceous gland, and intrafollicular hypercornification that induces follicular obstruction. Effective treatment directed against the colonization of bacteria (*P. acnes*) in follicles has made use of anti-infectives such as topical benzoyl peroxide (2.5%-10%), clindamycin, and erythromycin and systemic tetracyclines; however, known disadvantages to this treatment modality include irritation and limited use due to pathogen resistance [2-5]. Effective treatment directed towards inhibiting sebaceous gland activity has included oral corticosteroids, spironolactone, and isotretinoin in addition to anti-androgens (eg, cyproterone acetate). Known disadvantages to this treatment modality include being limited to use in females (anti-androgens), and limited to short term use for safety (oral corticosteroids). Finally, effective treatment directed against intrafollicular hypercornification has made use of retinoids such as oral isotretinoin and topical tretinoin or isotretinoin to regulate the intrafollicular keratinization process, inhibiting follicular hyperkeratinization and follicular obstruction [6]. In general, the known usefulness of oral retinoids (ie, oral isotretinoin) is limited by their side effects, which range from relatively minor effects (eg, dryness of mucosa and skin, skin irritation, and skin scaling) to major toxicity syndromes (reversible hair loss, bone toxicity and teratogenicity) and may include varying degrees of symptoms associated with hypervitaminosis A syndrome [2, 7, 8]. Likewise, the efficacy of topical retinoids such as tretinoin or isotretinoin may be limited by the known side effects, which include significant erythema, dryness, peeling, scaling, and irritation [9].

Tretinoin and benzoyl peroxide are retinoid prodrugs that activate 3 members of the retinoid acid receptor (RAR) nuclear receptors (RARα, RARβ, and RARγ), which act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation. Tretinoin and benzoyl peroxide show a relative selectivity for RARβ, and RARγ. It has not been established, however, whether the clinical effects of tretinoin and benzoyl peroxide are mediated through activation of RARs, other mechanisms, or both. Although the mechanism of action for tretinoin and benzoyl peroxide in the treatment of acne is unknown, the drug's antihyperproliferative, normalizing-of-differentiation, and anti-inflammatory effects may be related to the observed efficacy.

IDP-120 Gel is packaged in a dual-chamber airless pump, with each active gel contained in a separate cartridge. Specifically, one cartridge is filled with tretinoin (0.1%) gel, while the other is filled with BPO (5%) gel. The gels will be mixed (outside of the pump) immediately prior to topical application on affected skin. When combined, the gels dispensed from the pump will have a concentration of tretinoin, 0.05% (w/w) and BPO, 2.5% (w/w). This proposed product is the first gel formulation developed for tretinoin and benzoyl peroxide and will be evaluated for safety and effectiveness in treating acne vulgaris.

6 Study Objectives and Purpose

The primary objective of this study is to evaluate the safety, efficacy and tolerability of a once-daily topical application of IDP-120 Gel compared to IDP-120 Vehicle Gel in subjects with moderate to severe acne vulgaris (a score of 3 or 4 [moderate to severe] on the Evaluator's Global Severity Score (EGSS) scale).

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, efficacy and tolerability of IDP-120 Gel in comparison with IDP-120 Vehicle Gel. To be eligible for the study, subjects must be at least 9 years of age and older and have a clinical diagnosis of moderate to severe acne vulgaris (a score of 3 or 4 [moderate to severe] on the EGSS scale).

Approximately 600 subjects will be enrolled into this study and randomized into one (1) of two (2) treatment groups:

- 300 subjects in the IDP-120 Gel, once-daily application group
- 300 subjects in the IDP-120 Vehicle Gel, once-daily application group

Subjects will be enrolled at approximately 24-35 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).

An interactive web based response system (IWRS) will be employed to facilitate randomization of study subjects. Treatment assignments and study drug kit numbers will be generated centrally by the IWRS. At each clinical site, 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 week 12 visit) with the exception of study visit days (Baseline, Weeks 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 applied at the investigational center as per instruction from the study coordinator or designee. The subjects will be instructed to avoid exposure to direct sunlight to prevent sunburn and should be instructed to use sunscreens of at least SPF 15 and wear protective clothing (e.g., hat). 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 (only Weeks 4 and 8; 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.

Subjects will be asked to complete the Acne-Specific Quality of Life Questionnaire (Acne-QoL, Appendix 17.3). The Acne-QoL will be completed at Baseline and Week 12. Inferential statistical analysis will not be performed on the questionnaire; the subjective responses will be compared between treatment groups for trends.

The EGSS should be completed prior to the lesion counts.

Information on reported and observed adverse events (AEs) will be obtained at each visit. An abbreviated physical examination and vital sign measurements will be performed at Baseline and Week 12 Visits (final visit) for all subjects.

For all pre-menses females and female subjects of childbearing potential, urine pregnancy testing will be performed at Screening and confirmed at Baseline prior to randomization, and at Weeks 2, 4, 8 and 12. Serum pregnancy tests will also be conducted at Baseline and Week 12 / early termination.

Safety laboratory testing will be conducted at Baseline and Week 12 / early termination.

Subjects who terminate 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.

A “Re-screened” subject (e.g., subject that is rescreened beyond the allowed screening period window) will be considered a new subject and will need to be re-consented, receive a new screening number, and be entered in IWRS as a new subject. All screening assessments for re-screened subjects will need to be completed.

Table 1. Study Design and Schedule of Assessments

PROCEDURES	VISIT 1[1] 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[5] Week 12 (Day 84 -3/+5 days)
Informed consent/Assent	X					
Obtain Subject Number from IWRS	X					
Demographics	X					
Medical history[2]	X	X				
Inclusion/Exclusion criteria[2]	X	X				
Previous therapies[2]	X	X				
Acne-QoL		X				X
Pregnancy Test (pre-menses & FOCBP)[4]	X	X	X	X	X	X
Abbreviated physical examination[3]		X				X
Vital sign measurements		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
Photographs (select sites only)		X	X	X	X	X
Cutaneous Safety Evaluation		X	X	X	X	X
Tolerability Evaluation		X	X	X	X	X
Randomization in IWRS (obtain kit #)		X		X	X	
Administer Subject Instructions (Appendix 17.1)		X				
Dispense Study Drug (one IWRS-assigned pump)		X		X	X	
Weigh Study Drug to the nearest 0.1gram		X	X	X	X	X
Study Drug applied at investigational center		X	X	X	X	
Study Drug Collected				X	X	X
Subject Diary Calendar dispensed		X	X	X	X	
Subject Compliance Reviewed / Diary			X	X	X	X
Adverse Events	X	X	X	X	X	X
Concomitant Therapy and Prohibited Therapies Review	X	X	X	X	X	X
End of Study						X

[1] 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.
[2] Update at baseline visit prior to randomization.
[3] Height will be measured at baseline only; weight measurements and examinations of other abbreviated physical parameters will be performed at Baseline and Week 12.
[4] For pre-menses females and FOCBP, the urine pregnancy test must be completed at all scheduled visits, as per schedule. 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.
[5] All Week 12 procedures should be completed for all subjects who terminate early.

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 9 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 a score of 3 (moderate) or 4 (severe) on the Evaluator's Global Severity Score (EGSS) assessment at the baseline visit;
4. Subjects with facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 20 but no more than 50;
5. Subjects with facial acne non-inflammatory lesion (open and closed comedones) count no less than 25 but no more than 100;
6. Subjects with two or fewer facial nodules;
7. Females of childbearing potential[1] and females who are pre-menses must be willing to practice effective contraception for the duration of the study. (Effective contraception is defined as stabilized on oral contraceptive for at least 3 months, IUD, condom with spermicidal, diaphragm with spermicidal, implant, Nuvaring, injection, transdermal patch, abstinence or sterile partner.) Females on hormonal contraceptive must have taken the same type for at least three months prior to entering the study and must not change type during the study. Those who have used hormonal contraception in the past must have discontinued usage at least three months prior to the start of the study. Women who use birth control for acne control only should be excluded.
8. Pre-menses females and females of childbearing potential must have a negative urine pregnancy test[2] at the screening and baseline visits;
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

[1] Pre-menses females and Females of Child Bearing Potential (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 (HRT) with documented plasma follicle-stimulating hormone (FSH) level >35mLU/mL]. Even women who are using oral, implanted or, injectable contraceptive hormones, an intrauterine device (IUD), barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, practicing abstinence or where partner is sterile (e.g., 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.

moisturizer/sunscreen combination products (see Appendix 17.2). The subject must agree to use non-comedogenic products (including makeup and shaving products).

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, make-up, soap, masks, washes, sunscreens, etc) to their face;
8. Female subjects who are pregnant, nursing mothers, planning a pregnancy during the course of the trial, or become pregnant during the study;
9. Use of hormones (eg, Depogen, Depo-Testadiol, Gynogen, Valergen, etc) for less than 12 weeks immediately preceding study entry; Subjects treated with hormones 12 or more consecutive weeks immediately prior to study entry need not be excluded unless the subject expects to change dose, drug or discontinue hormone use during the study;
10. If female, subject has a history of hirsutism, polycystic ovarian disease or clinically significant menstrual irregularities;
11. 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;
12. 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 mid-to super-high potency corticosteroids, phenytoin and phenobarbital); Multivitamins, including Vitamin A at recommended daily doses and Vitamin D at stable doses, are acceptable;
13. 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 tretinoin and benzoyl peroxide;

14. Concomitant use of potentially irritating over-the-counter products that contain ingredients such as benzoyl peroxide, alpha-hydroxy acid, salicylic acid, retinol or glycolic acids;
15. Subjects who have not undergone the specified washout period(s) for the following topical preparations or 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 (including comedone removal strips) 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 (e.g., BPO, salicylic acid)	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
Facial procedures, including chemical peel, microdermabrasion, light (LED, PDT) and laser therapy, and acne surgery	4 weeks

If the subject requires topical treatment for acne on areas other than the face (e.g., chest and/or back), the investigator may prescribe a product that does not contain tretinoin or BPO and must be noted in source documents and eCRF;

16. 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

17. Subject intends to use a tanning booth or sunbathe during the study;
18. Subjects who are unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function;
19. Subjects with any underlying disease that the Investigator deems uncontrolled, and poses a concern for the subjects 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 (e.g., 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/electronic case report forms (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 at least twice to reach the subject by telephone, email and/or text message and will send a follow-up letter by certified mail before considering the subject lost to follow-up. These actions will be reported on the End of Study source documents, and a copy of the follow-up letter maintained in the investigator's file.

All premature discontinuations and their 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 a subject number assigned can be replaced by another if they discontinue 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 AE form.

Death – Complete 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 at least 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 pregnancy and SAE forms if applicable and report to the same contacts using the same reporting procedure for an SAE under Section 11.4.6.

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. Consent withdrawal, subject moved, schedule conflicts.

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

Other – Specify in comments section of final eCRF.

Subjects who terminate treatment 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-blinded study, in which the identity of the study drug will be unknown to investigator/evaluator and subjects, as well as all individuals closely associated with the study.

Subjects will be randomized to 1 of the 2 treatment groups in a ratio of 1:1 (IDP-120 [tretinoin 0.05% and benzoyl peroxide 2.5%] Gel: IDP-120 Vehicle Gel). Each screened subject will be assigned a unique 6-digit study subject number assigned by the investigational center, which will consist of the 3-digit investigational center/site number (pre-assigned by sponsor/designee) and the 3-digit chronological screening order number, starting with 001 (e.g., 101001, 101002). The study drug kits will be assigned to subjects based on a randomization code, and a kit will be dispensed to the subjects by the IRWS at Baseline, Week 4 and Week 8 visits. A study drug log will document the inventory and dispensing of study drug at each investigational center.

9.2 Randomization and Blinding

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

As a double-blinded study, the investigators, the site 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 investigational 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 verified, entered into the database, and validated; subject evaluability assessments are performed and entered into the database; 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 IWRS. 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 or physical treatments on the face that have a known beneficial effect for acne vulgaris:

Topical astringents and abrasives (including comedone removal strips) on 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 (e.g., BPO, salicylic acid)	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
Facial procedures, including chemical peel, microdermabrasion, light (PDT, LED) and laser therapy, and acne surgery	4 weeks

If the subject requires topical treatment for acne on areas other than the face (e.g., chest and/or back), the investigator may prescribe a product that does not contain tretinoin or BPO, and note in the source documents and eCRF.

In addition there is a mandatory wash out period and restrictions 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 medications or 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. No other topical and/or physical treatment (except as noted above) other than the study drug will be permitted for acne.

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, either over the counter (OTC) or prescription, used by the subject will be considered concomitant medication (e.g., aspirin, Tylenol, birth control pills, vitamins). Every attempt should be made to keep concomitant medication and therapy dosing constant during the study. Any change to concomitant medication or 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 non-medicated will be captured on the Concomitant Therapy source document and eCRF. Subjects must use Investigator approved cleansers, moisturizers, and sunscreens.

Subjects should avoid excessive UV exposure by such activities as sun bathing or tanning booths. Subjects should be instructed to use sunscreens of at least SPF 15 and wear protective clothing during the day (e.g., hat). In addition, subjects should be instructed to not use study drug on skin that may have become eczematous (on the face) during the course of the study.

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, he or she will be instructed to return it as soon as possible. The subjects will bring the pumps dispensed at each treatment visit to the next subsequent study visit. Each pump will be weighed on a calibrated scale (with the cap on) to the nearest 0.1 gram by a study coordinator or designee prior to dispensation and after collection. The subject will also be asked to complete a diary calendar and questioned regarding the study drug use since the previous visit in order to judge the subject's compliance with applying the study drug. A subject who deviates significantly 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 IRB/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 nonadherence to the protocol that results in a significant, additional risk to the subject, when the subject or investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria) and the subject was enrolled without prior sponsor approval, or when there is nonadherence to FDA regulations and/or ICH GCP guidelines.

The investigator or designee must document and explain in the subjects' source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects 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) 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-120 Gel, and IDP-120 Vehicle Gel

Chemical structure and formula for the active ingredients in IDP-120 Gel and IDP-120 Vehicle Gel are listed in the tables below:

Table 2. Drug Substances Identification

Active Ingredient	Tretinoin 0.05%
Chemical Name	all-trans-retinoic acid: (all E)-3,7-Dimethy-9-(2,6,6-trimethy-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid 2,4,6,8-Nonatetraenoic acid-3,7-dimethy-9-(2,6,6-trimethyl-1-cyclohexen-1-yl) (all E)
Chemical Class	Retinoid
Molecular Formula	$C_{20}H_{28}O_2$
CAS Registry Number	302-79-4

Active Ingredient	Benzoyl Peroxide, 2.5%
Chemical Name	Peroxide, Dibenzoyl
Chemical Class	Peroxide
Molecular Formula	$C_{14}H_{10}O_4$
CAS Registry Number	94-36-0

Table 3. Test Product Identification

	Investigational Products	Vehicle
	IDP-120 Gel	IDP-120 Vehicle Gel
Name of Active Ingredient	Tretinoin and benzoyl peroxide	N/A
Drug Name / Formulation/ Concentration	IDP-120 Gel (tretinoin 0.05 % and benzoyl peroxide 2.5%)	IDP-120 Vehicle Gel
Manufacturer	Bausch Health Companies, Inc. 2150 St. Elzear Blvd West Laval (Quebec), Canada H7L 4A8	
Packaging	30 g pump	
Storage Requirements	Store at 20°C to 25°C (68°F to 77°F)	
Appearance	White to off-white gel	
Dosing Schedule	Once daily x 12 weeks	
Route of Administration	Topical Application	

10.1.1 Packaging and Labeling

IDP-120 Gel and the IDP-120 Vehicle Gel will be supplied in subject kits. Instructions will be provided to the study drug technician responsible at the clinical sites. When a subject is randomized into the study, the kit number will be assigned to be used for that randomized subject by the IWRS. Each subject kit will contain one pump, which has 30 grams of study material. A new subject kit will be assigned to a subject at each of the following visits: Baseline, Week 4 and Week 8. The subjects will be dispensed one kit at Baseline as assigned in the IWRS. The pumps will be weighed on a calibrated scale (with the cap on) to the nearest 0.1 gram prior to dispensing. The subject will bring the pump to the next study visit (Week 2), where it will be collected and weighed to the nearest 0.1 gram – a new pump will not be dispensed at this visit. The subject will then bring the same pump to the subsequent study visit (Week 4), where it will be collected and weighed to the nearest 0.1 gram; one new pump will be dispensed again by the IWRS at Week 4, weighed 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 or damages the pump, a replacement kit will be dispensed via IWRS. Each pump dispensing will be documented on the drug accountability log.

Each subject kit (and pump) will have a double panel label. Labels may contain, at a minimum, the following information:

- Protocol Number

- Kit Number
- Contents
- Space for entry of the subject initials and subject number
- Space for entry of date dispensed
- The sponsor name, Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals N.A., LLC
- The quantity of product (30 grams)
- A statement reading, “For external use only. Avoid contact with eyes and lips”
- A statement reading, “Store at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F).”
- A statement reading, “Caution: New Drug Limited by Federal Law to Investigational Use”
- A statement reading, “Return this product to your investigational site at your next visit.”

10.1.2 Storage, Handling, and Disposal of Study Drug

The study drug should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F), and should not be refrigerated. All unused study drug will be sent back to the Sponsor or Sponsor designee upon study completion for documented disposal.

10.1.3 Administration

The assigned study drug will be applied topically to the face once a day at home, in the evening, for 12 weeks (up to the evening prior to week 12 visit), with the exception of study visit days (Baseline, Weeks 2, 4 and 8), where study drug will be applied by the subject after the study visit is completed at the investigational center. Study drug will be applied as a thin layer that is gently rubbed in to the skin. Study drug use will be limited to the face.

The Investigator and/or trained investigational center staff member will instruct the subject on the proper application procedure of the study drug to the treatment area at the Baseline visit (see Appendix 17.1). All subjects will be instructed to apply study drug at approximately the same time every day in the evening for 12 weeks (up to the evening before the Week 12 visit) after cleansing. On study visit days (Baseline, Weeks 2, 4 and 8) subjects should be instructed to wait until after their study visit is completed to apply study drug 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.

During daily application, subjects will be instructed to gently wash their face 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 face dry. The subjects should use the pump to dispense the study drug into their palm (two depressions of the pump into the palm of their hand). Study staff will highlight the importance of proper depression of the pump by using one or two fingers placed directly on the indented center of the pump head to dispense study product. Upon completing two depressions of the pump and with study product in the palm of their hand, subjects will be instructed to blend the two colored gels in their palm until one uniform color is observed. This blended gel should then be dotted on to 6 areas (chin, left cheek, right cheek, nose, left forehead, right forehead) on the face. 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. They should gently smooth the test material over the face evenly. The test material 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 investigational product to the face. Subjects should also be instructed to place the cap back onto the pump after every use.

The subjects will be instructed to continue using the same Sponsor/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 make-up 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 on the face. Subjects should be instructed to minimize sun exposure and to use Sponsor/Investigator-approved, non-medicated sunscreens of at least SPF 15 and to wear protective clothing during the day (e.g., hat). Subjects should also be instructed to not use study treatment on skin that may have become eczematous (on the face) during the course of the study.

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 site 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 investigational center staff member will conduct a complete inventory of study materials and assume responsibility for their storage and dispensing. In accordance with federal regulations,

the investigators must agree to keep all study materials in a secure location with restricted access. The Investigator will keep a record of the inventory and dispensing of all study drug. This record will be made available to the sponsor's monitor for the purpose of accounting for all clinical supplies. 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 to the nearest 0.1 gram (with the cap on) 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 as per sponsor's direction.

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 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 IWRS, which will consist of the 3-digit site number (pre-assigned to each site) and the 3-digit chronological order screening number, assigned by the IWRS and starting with 101 (eg, 101001, 101002, etc.; in this example site 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) for the past 4 weeks (past 6 months for systemic retinoids). Record any therapies that will be used concomitantly during the study.
6. Perform Evaluator's Global Severity Score (EGSS) assessment followed by inflammatory lesion count and non-inflammatory lesion count.
7. Perform a Urine Pregnancy Test for all females who are pre-menses and females of childbearing potential. The urine pregnancy tests will be supplied by the CRO or CRO

vendor. Verify that the subject meets the applicable inclusion/exclusion criteria as outlined in Sections 8.1 and 8.2.

8. Discuss allowed cleansers, moisturizers and sunscreens and record any cleanser, moisturizer and sunscreen use. (Appendix 17.2).
9. If subject wears makeup, remind the subject not to wear make-up during any future visits.
10. 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.

A urine pregnancy test must be completed at the Screening and Baseline visits prior to randomization, and 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, Baseline Visit (Visit 2) 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-Specific Quality of Life Questionnaire (Acne-QoL) will be completed by the subject and collected prior to any other study-related procedures.
2. Record any changes in medical history since screening.
3. 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.
4. Perform a Urine Pregnancy Test for all females who are pre-menses and females of childbearing potential. The urine pregnancy tests will be supplied by the CRO or CRO vendor.
5. Perform an abbreviated physical examination, including height and weight, and vital signs (blood pressure, heart rate, respiration rate and oral temperature). Note: height will only be measured at baseline, and not subsequent visits. Any abnormal physical exam findings will be recorded.
6. Verify that the subject continues to meet the applicable inclusion/exclusion criteria as outlined in Sections 8.1 and 8.2.
7. The Evaluator will perform Baseline efficacy evaluations including the Evaluator's Global Severity Score (EGSS), inflammatory lesion counts, and non-inflammatory lesion counts. 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. The Evaluator will perform Cutaneous Safety and Tolerability Evaluations.

9. Collect blood samples for routine laboratory analysis (CBC/Diff, serum chemistry, and serum pregnancy for pre-menses females and females of childbearing potential).
10. *Select Sites Only* – Obtain representative photographs of the face.
11. Assign the subject the presented kit number (this number will be generated from the Interactive Web Response System, [IWRS]).
12. The study coordinator or designee will weigh the pump (with the cap on) to the nearest 0.1 gram on a calibrated scale and dispense to the subject. A study diary calendar will also be dispensed and the subject will be instructed to bring it in for their subsequent visits.
13. 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 investigational 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 in the evening up to evening prior to Week 12 visit (study drug will not be applied in the evening after this study visit).
14. 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 (e.g., hat). Remind subject not to use study treatment on skin that may become eczematous during the study.
15. Record any AEs or changes in AEs since the screening visit and/or reported spontaneously by the subject.
16. Schedule the next study visit at Week 2 (Day 14 ± 3 days). Remind the subject to not apply study drug on day of next study visit, prior to the clinic 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, if possible):

1. The Evaluator will perform the efficacy evaluations including the Evaluator's Global Severity Score (EGSS), inflammatory lesion counts, 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 visit for the same subject.
2. The Evaluator will perform Cutaneous Safety and Tolerability Evaluations.
3. 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.

4. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
5. Perform a Urine Pregnancy Test for all females who are pre-menses and females of childbearing potential.
6. The study drug technician will retrieve and weigh the used study drug with the cap on to the nearest 0.1 gram. Note: a new pump will NOT be dispensed at this visit. The original pump will be re-dispensed back to the subject.
7. 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.
8. *Select Sites Only* – Obtain representative photographs of the face.
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 investigational 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).
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 (e.g., hat). Remind subject not to use study treatment on skin that may have become eczematous during the study.
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 Visit/Final Visit) procedures must be performed):

1. The Evaluator will perform the efficacy evaluations including the Evaluator's Global Severity Score (EGSS), inflammatory lesion counts, 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. The Evaluator will perform Cutaneous Safety and Tolerability Evaluations.
3. 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.
4. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.

5. Perform a Urine Pregnancy Test for all females who are pre-menses and females of childbearing potential.
6. The study drug technician will retrieve and weigh the used study drug pump with the cap on to the nearest 0.1 gram. Assign the subject another kit number (this number will be generated from the IWRS) and dispense a new subject kit of study drug. The new pump will be weighed on a calibrated scale with the cap on to the nearest 0.1 gram.
7. 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.
8. *Select Sites Only* – Obtain representative photographs of the face.
9. 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 investigational 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).
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 (e.g., hat). Remind subject not to use study treatment on skin that may have become eczematous during the study.
11. 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, if possible):

1. The Evaluator will perform the efficacy evaluations including the Evaluator's Global Severity Score (EGSS), inflammatory lesion counts, 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. The Evaluator will perform Cutaneous Safety and Tolerability Evaluations.
3. 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.
4. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
5. Perform a Urine Pregnancy Test for all females who are pre-menses and females of childbearing potential.

6. The study drug technician will retrieve and weigh the used study drug pump (with the cap on) to the nearest 0.1 gram. Assign the subject another kit number (this number will be generated from IWRS) and dispense a new subject kit of study drug. The new pump will be weighed on a calibrated scale with the cap on to the nearest 0.1 gram.
7. 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.
8. *Select Sites Only* – Obtain representative photographs of the face.
9. 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 investigational 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).
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 (e.g., hat). Remind subject not to use study treatment on skin that may have become eczematous during the study.
11. Schedule the next study visit at Week 12 (Day 84 -3/+5 days). Remind the subject to apply study drug up to evening prior to Week 12 visit and 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 Treatment/Study Visit

The following procedures will be conducted at this visit:

1. The Week 12 Acne-QoL will be completed by the subject and collected prior to any other study-related procedures.
2. Perform an abbreviated physical exam, including measurements of weight and vital signs (blood pressure, heart rate, respiration rate, and oral temperature). Any abnormal physical exam findings will be recorded.
3. The Evaluator will perform the efficacy evaluations including the Evaluator's Global Severity Score (EGSS), inflammatory lesion counts, 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. The Evaluator will perform Cutaneous Safety and Tolerability Evaluations.
5. 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.
6. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.

7. The study diary calendar will be collected and reviewed for compliance. Any missed doses or deviations should be reported.
8. The study drug technician will retrieve the study drug pump from the subject and weigh the pump (with the cap on) on a calibrated scale and record the weight to the nearest 0.1 gram.
9. Perform a Urine Pregnancy Test for all females who are pre-menses and females of childbearing potential.
10. Collect blood samples for routine laboratory analysis (CBC/Diff, serum chemistry, and serum pregnancy for pre-menses females and females of childbearing potential).
11. *Select Sites Only* – Obtain representative photographs of the face.
12. 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 scores and lesion counts will be performed at each study visit. The EGSS scores 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, every effort must be made for the same Evaluator to assess the Subject at both the Baseline and Week 12 visits.

11.2.1 Evaluator's Global Severity Score (EGSS)

The Evaluator's Global Severity Score (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 with a global severity of a 3 (moderate) or a 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

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 one 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 lesions counts will be collected at each visit and/or upon discontinuation. 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 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

11.2.3 Other Assessments

Photography

At select sites, photographs of the face will be taken at Baseline and at Weeks 2, 4, 8 and 12. Only subjects who provide written photographic consent for facial photographs will be included in photography.

11.3 Evaluation of Safety

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

11.3.1 Cutaneous Safety Evaluations

Cutaneous safety will be evaluated through assessment of scaling, erythema, hypo-pigmentation and hyper-pigmentation at the drug-application site at the time of the visit. Cutaneous tolerability will be evaluated through assessment of selected local signs and symptoms at the drug-application site: itching, burning and stinging, as an average since the last visit.

Cutaneous safety and 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.

(Note: To be assessed by the evaluator at the time of the study visit.)

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

Hypo-pigmentation:

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

Hyper-pigmentation:

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

11.3.2 Tolerability Evaluations

To be reviewed with the subject at the study visit as average over the period since the previous visit.

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 two or more years before Baseline need not be collected unless considered relevant by the investigator.

An abbreviated physical examination including measurements of height and weight, and vital signs (blood pressure, heart rate, respiration rate, and oral temperature) will be performed at Baseline and Week 12 (end of treatment/study). Any abnormal physical exam findings will be recorded. Note: Height measurement will only be performed at Baseline.

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 visit. 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 investigative site and filed in the subject's documentation.

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

11.3.5 Pregnancy Tests

All pre-menses females and female subjects of childbearing potential will undergo serum pregnancy testing at Baseline and Week 12. In addition, urine pregnancy testing will be performed 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 or CRO vendor.

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. AEs include any illness, sign, symptom, or out-of-range and clinically significant laboratory finding that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the study. The collection of non-serious AEs and serious adverse events (SAEs) 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 drug-related. All AEs, whether in response to a query, observed by the study site 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 (or up to 30 days after final study visit).

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Cutaneous 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 name (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 abnormalities are to be recorded as AEs only if they are clinically significant (for example: are symptomatic, requiring corrective treatment, leading to discontinuation or fulfilling a seriousness criterion).

11.4.3 Serious Adverse Events

All AEs will be assessed as either serious or non-serious.

An SAE or serious adverse event 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, elective abortion and an ectopic pregnancy will be considered SAEs, and must be reported per Reporting of SAEs 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: Awareness of a sign of symptom but is easily tolerated, requires no treatment and does not interfere with subject's daily activities
- Moderate: Low level of concern to the subject and may interfere with daily activities, but can be relieved by simple therapeutic care
- Severe: Interrupts the subject's daily activity and requires systemic or other treatment

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.

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 investigational 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 confirmed facsimile or email 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.

The contact(s) for reporting an SAE are:

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 investigational

product) 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 autopsy or 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/or facsimile/email) of all subject deaths. Written follow-up must be received by the medical monitor and the Institutional Review Board/Independent Ethics Committee (IRB/IEC) within five (5) calendar days of initial notification.

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 confirmed facsimile transmission/email to the Medical Monitor and Sponsor and/or Sponsor designee.

11.4.7 Expedited Serious Adverse Event Reports

An AE, whether serious or non-serious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator Brochure or if the event is of greater frequency, specificity or severity.

Expedited SAE reports are those that are both unexpected based on the reference document (Investigator Brochure) and are related (ie, the relationship cannot be ruled out) to the study drug. These expedited reports are subject to reporting timelines of 7 and/or 15 calendar days to the regulatory reporting agency(ies). The Sponsor will notify regulatory authorities of these AEs and all participating investigational centers in writing for submission by the investigator to the IRB/IEC. This notification will be in the form of a Safety Update to the Investigator Brochure (ie, "15-day letter").

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 and IRB/IEC will determine if the informed consent requires revision. 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 female subjects of childbearing potential 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 female subject of childbearing potential in this clinical trial, 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 before study enrollment.

During the study, all female subjects of childbearing potential 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 treatment, 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.

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. If a pregnancy is associated with an SAE, the event should be reported on an SAE form and a pregnancy form as per procedure outlined in Section 11.4.6.

12 Statistics

All statistical processing will be performed using SAS® version 9.3 or later unless otherwise stated. Statistical significance will be based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less.

The primary method of handling missing efficacy data will be based on estimation using the method of Markov Chain Monte Carlo (MCMC) imputation. This method provides robust estimation when the pattern of missingness is arbitrary. Additionally, the 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 comparative analyses and subsequent imputation result inference with SAS PROC MIANALYZE. Descriptive statistics will also be derived from the multiply imputed datasets.

Additionally, a model-based multiple imputation process will be used as a sensitivity analysis to the MCMC imputation. The absolute change in lesion count will also be analyzed using a repeated measures ANCOVA for lesion count data or a repeated measures logistic regression model (generalized estimating equations) for the dichotomized EGSS. Finally, a tipping point analysis will be performed for the primary endpoints.

A statistical analysis plan (SAP), 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.

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

All assessments will be conducted for both ITT and PP.

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 in inflammatory lesion count from Baseline to Week 12
- Absolute change in non-inflammatory lesion count from Baseline to Week 12
- Percentage of subjects who achieve at least a two-grade reduction at Week 12 from Baseline in the Evaluator's Global Severity Score and were Clear or Almost Clear

12.1.2 Secondary Efficacy

The secondary efficacy endpoints will be the following:

- Percent change in non-inflammatory lesion count from Baseline to Week 12

- Percent change in inflammatory lesion count from Baseline to Week 12
- Percentage of subjects who have at least a 2 grade reduction at Week 12 from Baseline in the Evaluator's Global Severity Score
- Percent change in non-inflammatory lesion count from Baseline to Week 8
- Percent change in inflammatory lesion count from Baseline to Week 8
- Percent change in non-inflammatory lesion count from Baseline to Week 4
- Percent change in inflammatory lesion count from Baseline to Week 4

12.1.3 Supportive Efficacy

The supportive efficacy endpoints will be as follows:

- Percent change in non-inflammatory lesion count from Baseline to Week 2
- Percent change in inflammatory lesion count from Baseline to Week 2
- Percentage of subjects who have at least a 2 grade reduction at Week 8 from Baseline in the Evaluator's Global Severity Score
- Percentage of subjects who have at least a 2 grade reduction at Week 4 from Baseline in the Evaluator's Global Severity Score
- Percentage of subjects who have at least a 2 grade reduction at Week 2 from Baseline in the Evaluator's Global Severity Score

12.1.4 Test of Superiority for Lesion Count Variables

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 either parametric or non-parametric methods consistent with the statistical assumptions required to support the analyses. Specifically, the tests of superiority will be based on an ANCOVA with factors of treatment and analysis center and the respective Baseline lesion count as a covariate or on ranked data submitted to 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.

A skewness test, based on the methods presented by J.H. Zar (1984) [10], will be applied to the residuals resulting from an ANCOVA. A two-sided p-value for the skewness test significant at 0.01 will imply the use of the non-parametric method. If a parametric analysis is indicated, the results of the parametric analysis will be considered the primary analysis. Should a non-parametric analysis be indicated, the absolute or percent changes in inflammatory and non-inflammatory lesions will be rank transformed prior to submitting them to the ANCOVA. Results of the rank-transformed analyses then will be considered the primary analysis; however, results of the non-ranked transformed analyses will also be presented.

12.1.5 Test of Superiority for EGSS

The EGSS will be dichotomized into “success” and “failure” with a subject considered a success for those visits if the Evaluator’s Global Severity Score is at least 2 grades less than Baseline and are Clear or Almost Clear. The analysis of the dichotomized Evaluator's Global Severity Score will be based on a logistic regression test with factors of treatment group and analysis center.

12.1.6 Statistical Hypothesis Testing and Control of Multiplicity

Statistical hypothesis testing for lesion count analyses will use the statistical model introduced in Section 12.1.4 and employs the methods of Section 12.1.9 regarding missing values. The analysis of the dichotomized Evaluator's Global Severity Score will be based on the logistic regression with factors of treatment group and analysis center and employs the methods of Section 12.1.9 regarding missing values.

The overall Type I error will be controlled by requiring the three co-primary efficacy endpoints to be statistically significant. Specifically, failure of any one of the primary efficacy endpoints will invalidate the statistical significance of the secondary efficacy endpoints.

The following stepwise process will be conducted for testing the secondary efficacy endpoints in order to control for multiplicity. These tests will be performed for only the ITT population. The testing process will terminate whenever a statistical test for a step is not significant. All subsequent tests for the remaining steps will be considered not significant. The order of testing is:

Step Number	Secondary Endpoint
1	Percent change in non-inflammatory lesion count from Baseline to Week 12
2	Percent change in inflammatory lesion count from Baseline to Week 12
3	Percentage of subjects who have at least a 2 grade reduction at Week 12 from Baseline in the Evaluator's Global Severity Score
4	Percent change in non-inflammatory lesion count from Baseline to Week 8
5	Percent change in inflammatory lesion count from Baseline to Week 8
6	Percent change in non-inflammatory lesion count from Baseline to Week 4
7	Percent change in inflammatory lesion count from Baseline to Week 4

The following stepwise process will be conducted for testing the supportive efficacy endpoints in order to control for multiplicity. These tests will be performed for only the ITT population. In order to control for multiplicity, failure of any one of the secondary efficacy endpoints will invalidate the statistical significance of the supportive efficacy endpoints. The testing process

will terminate whenever a statistical test for a step is not significant. All subsequent tests for the remaining steps will be considered not significant. The order of testing is:

Step Number	Supportive Endpoint
1	Percent change in non-inflammatory lesion count from Baseline to Week 2
2	Percent change in inflammatory lesion count from Baseline to Week 2
3	Percentage of subjects who have at least a 2 grade reduction at Week 8 from Baseline in the Evaluator's Global Severity Score
4	Percentage of subjects who have at least a 2 grade reduction at Week 4 from Baseline in the Evaluator's Global Severity Score
5	Percentage of subjects who have at least a 2 grade reduction at Week 2 from Baseline in the Evaluator's Global Severity Score

12.1.7 Descriptive Statistics

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

- Frequency and percent distributions of the Evaluator’s Global Severity Score at Baseline and Weeks 2, 4, 8, and 12.
- Frequency and percent distributions of the dichotomized Evaluator’s Global Severity Score at Baseline and 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.

12.1.8 Pooling Analysis

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 5 subjects will be enrolled in each treatment arm for any investigator. In the event that there are too few subjects in a treatment arm 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 5 subjects per treatment arm. 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 (unranked or ranked) 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.

12.1.9 Missing Efficacy Data Imputations

Lesion Count Variable Missing Data Imputation

Missing 12 week data will be estimated by multiple imputation and subsequently analyzed. Missing lesion count data will be derived for the analysis using the method of MCMC multiple imputation which does not rely on the assumption of data missing at random. Additionally, the pattern of missing observations in each treatment group cannot 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 3 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, or 2);
mcmc chain=multiple;
var baseline week2 week4 week8 week12;
run;
```

2. 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.
3. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 4 random seeds will be needed to impute inflammatory lesion counts and non-inflammatory lesion counts for the two treatment groups. Those 4 random seeds have been pre-specified by using a random number generator:

- Inflammatory Lesion Counts; IDP-120 Gel: Seed= 34116691
- Inflammatory Lesion Counts; IDP-120 Vehicle: Seed= 1806432384
- Non-Inflammatory Lesion Counts; IDP-120 Gel: Seed= 2049678471
- Non-Inflammatory Lesion Counts; IDP-120 Vehicle: Seed= 655282615

EGSS Missing Data Imputation

A similar procedure will be used for the analyses based on percentage of EGSS successes wherein the ANCOVA analysis is replaced with a logistic regression analysis. Specifically, missing 12 week EGSS values from which the dichotomized EGSS is derived will be estimated by MCMC which does not rely on the assumption of data missing at random. Additionally, the pattern of missing observations in each treatment group cannot influence the missing value estimation in the other because the imputation is being conducted independently for each treatment group.

The missing 12-week 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 3 principal tasks:

1. 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, or 2);
```

```
  mcmc chain=multiple;
  var baseline week2 week4 week8 week12;
run;
```

2. 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 2 random seeds will be needed to impute EGSS for the two treatment groups. Those 2 random seeds have been pre-specified by using a random number generator:

- EGSS; IDP-120 Gel: Seed= 923694678
- EGSS; IDP-120 Vehicle: Seed= 802843905

12.1.10 Sensitivity Efficacy Analyses

Sensitivity analyses for absolute change in lesion count

The first sensitivity analysis for absolute change in lesion count will use a repeated measures ANCOVA, with treatment, analysis center, and visit (ie, Week 4, Week 8) as independent factors and a covariate of baseline lesion count. In this analysis, data from all post-baseline visits will be included with no imputation for missing data.

The second sensitivity analysis will use the model based multiple imputation method to impute missing data for the absolute change in lesion counts at Week 12. Although the full details will be presented in the SAP, the multiple imputation will involve 3 principal tasks:

1. Missing values will be filled in 5 times to generate 5 data sets. The imputation model used will be an ANCOVA with factors of treatment group and analysis center, and a covariate of baseline lesion count (ie, the imputation model will be the same as the analysis model). Appropriate modifications will be made should the analysis be based on a non-parametric method.
2. Each complete data set will be analyzed with an ANCOVA with factors of treatment group, and analysis center, and a covariate of baseline lesion count.
3. Results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 2 random seeds will be needed. Those 2 random seeds have been pre-specified by using a random number generator:

- Inflammatory Lesion Counts: Seed= 1792696133
- Non-Inflammatory Lesion Counts: Seed= 1438330601

Sensitivity analyses for EGSS

The first sensitivity analysis for the dichotomized EGSS success will use a repeated measures logistic regression model (generalized estimating equations), with dichotomized EGSS success as the dependent variable and treatment, analysis center, and visit (ie, Week 4, Week 8) as independent factors. In this analysis, data from all post-baseline visits will be included with no imputation for missing data.

The second sensitivity analysis will use the model based multiple imputation method to impute missing data for the dichotomized EGSS data. Although the full details will be presented in the SAP, the multiple imputation will involve 3 principal tasks:

1. Missing values will be filled in 5 times to generate 5 data sets. The imputation model used logistic regression with factors of treatment group and analysis center (ie, the imputation model will be the same as the analysis model).
2. Each complete data set will be analyzed with a logistic regression a factors of treatment group and analysis center.
3. Results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 1 random seed will be needed. The random seed has been pre-specified by using a random number generator:

- EGSS: Seed= 461039866

Tipping Point Analysis

A tipping point analysis of each primary endpoint will be performed as a sensitivity analysis for the handling of missing data.

12.1.11Subgroup Analyses

Subset analyses will be conducted for the ITT populations for the subgroups of baseline global severity, gender, age, ethnicity, and race. Age will be dichotomized to less than the median age of subjects and greater than or equal to the median age of subjects. An additional analysis will include age with categories of less than 18 and greater than or equal to 18. Subset analyses will be conducted on the variables absolute change from baseline in inflammatory lesions and non-inflammatory lesions at Week 12 as well as the dichotomized global severity score at Week 12. These analyses will contain only descriptive statistics.

12.1.12Subject 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

Safety will be evaluated by tabulations of adverse events (AEs), Cutaneous Safety Evaluation, and Tolerability Evaluations. Cutaneous Safety Evaluation scores (erythema, scaling, and 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. 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 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. All reported treatment-emergent AEs (TEAEs) will be summarized by the number of Subjects reporting AEs, system organ class, preferred term, severity, seriousness, and relationship to study drug. TEAEs are those AEs with an onset on or after the date of the first study drug application.

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 adverse events 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 adverse events 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 any treatment group.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim 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.

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

Vital signs as well as changes from Baseline in vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits.

12.2.4 Concomitant Medications

All recorded prior and concomitant medications will be classified based on terminology from the 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 treatment group for the ITT, PP, and safety populations. For continuous variables (e.g., age) comparisons among the two treatment groups will be conducted using a two-way analysis of variance (ANOVA) with factors of treatment group and analysis center. Ethnicity and race will be analyzed with a Cochran-Mantel-Haenszel test stratified by analysis center. Past and current medical conditions, as well as history of disease will be presented in a data listing.

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 presented 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 Populations

Approximately 600 subjects at least 9 years of age and older with moderate or severe acne (a score of 3 or 4 [moderate to severe] on the EGSS scale) will be enrolled and randomized in the study. With a 1:1 randomization ratio, it is anticipated that:

- 300 subjects will be randomized to receive IDP-120 Gel, once-daily application
- 300 subjects will be randomized to receive IDP-120 Vehicle Gel, once-daily application

The intent-to-treat (ITT) population will consist of all randomized subjects who were dispensed study drug. The safety population will be comprised of all randomized subjects who are confirmed to have used the study drug at least once.

An ITT analysis will be conducted as well as a per-protocol (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 treatment or the precise evaluation of treatment efficacy). The PP population will include subjects in the safety 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;
- Missed more than 1 post baseline visit prior to Week 12;
- Have not been compliant with the dosing regimen (i.e., Subjects may not miss more than five 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 trial that result in noteworthy study protocol violations.

12.8.2 Sample Size Determination

These power calculations are based primarily on the observed Week 12 results of the Phase 2 study, V01-120A-201. This study was a four-arm trial including IDP-120 Gel versus its individual gel components and Vehicle Gel and is therefore a relevant study for powering the current study.

A sample size of 300 per treatment arm has greater than 99% power to detect a statistically significant difference in non-inflammatory lesions with a significance level of 0.05. The estimated absolute change from baseline in treatment means were 13.3 and 8.7 for IDP-120 Gel versus its Vehicle gel, respectively, with a standard deviation of 11.0.

A sample size of 300 per treatment arm has greater than 99% power to detect a statistically significant difference in non-inflammatory lesions with a significance level of 0.05 using the estimated absolute change from baseline in treatment means of 18.8 and 7.8 for IDP-120 Gel versus its Vehicle Gel, respectively, with a standard deviation of 16.4.

In order to achieve at least 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 are Clear or Almost Clear with a significance level of 0.05, a sample size of 293 per treatment group is required. The estimated percentages with a 2 grade reduction at Week 12 from Baseline in the EGSS and Clear or Almost Clear are 26.6% and 14.3% for IDP-120 Gel versus its Vehicle Gel respectively. For simplicity, a sample size of 300 per treatment arm will be used.

12.8.3 Handling of Missing Data

The method of multiple imputation will be used (see Section 12.1.9).

12.8.4 Multicenter Issues

The study will be conducted at multiple investigational centers in North America and Latin America with the intention of pooling the results for analysis. Site specific data summaries, however, will be presented.

12.8.5 Multiplicity Issues

The overall Type I error will be controlled by requiring the three co-primary efficacy endpoints to be statistically significant. Specifically, failure of any one of the primary efficacy endpoints will invalidate the statistical significance of the secondary efficacy endpoints. See Section 12.1.6 for further detail.

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 sponsor and/or its designee. During this meeting, an extensive review and discussion of the protocol, role(s) of the study personnel, 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 utilized. During the course of the study, all data will be 100% source document verified by the monitors. All subject source records 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 Valeant in conformation with all appropriate local and federal regulations, as well as ICH guidelines. Interim and end of study audits of raw data, study files, and final report may be conducted by Valeant’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 investigational centers, source data/documents, CRFs, 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 unique subject number.

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/IEC 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

This protocol, proposed informed consent form and other information to subjects, and all appropriate amendments will be properly reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC). A signed and dated notification of the IRB/IEC approval will be provided to the sponsor and investigator prior to study initiation. 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

Written informed consent/assent, in accordance with local clinical investigation regulations, must be obtained prior to participation in the study. 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 form. 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 has been obtained. The original signed and dated informed consent form will be retained with the study records, and a copy of the signed form will be given to the subject.

An informed consent template will be supplied by the sponsor or designee. Any changes to the informed consent form must be agreed to by the sponsor or designee prior to submission to the IRB/IEC, and a copy of the approved version must be provided to the sponsor or designee after IRB/IEC approval.

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. It is acknowledged that subject initials, demographics (including birthdates), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study participants. 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.

14.7 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 Good Clinical Practice (GCP).

14.8 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 before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

14.9 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 (e.g., 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 was obtained
- Evidence that the subject meets study eligibility requirements (e.g., 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/therapies 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.

16 References

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17 Appendices

17.1 Subject Instruction Sheet

Overview of Product:

IDP-120 gel is supplied in a white pump with a white cap (**Figure 1a**). Once the cap is removed, the pump head with two dispensing nozzles will be exposed (**Figure 1b**).

Figure 1a

Figure 1b

Figure 1a: Front view of white pump with white cap
Figure 1b: Front view of pump with cap removed, exposing the two dispensing nozzles in the center.

Instructions:

- Wash hands and face with a gentle cleanser (as allowed by your study doctor).
- Hold the pump in one hand and place one or two fingers in the center of the pump head directly on top of the nozzles (**Figure 2a**).
- Hold the pump at an incline onto the palm of your hand (**Figure 2b**).
- Push the pump head down completely by pressing on center of the pump head (**Figure 2c**).

Figure 2a

Figure 2b

Figure 2c

Figure 2a: Front view of pump with finger over the nozzles (center of the pump)
Figure 2b: Pump held at an incline on to the palm
Figure 2c: Front view with fully depressed pump head (note the nozzles are lower than Figure 2a due to the pump being pushed down)

- First Time Use of New Pump ("Priming")
  - Priming occurs when a new pump is used – product may not immediately come out evenly, or at all, during the first depression (pressing) of the pump head. This is normal.
  - Priming will be performed during scheduled on-site clinic visits where new pumps will be dispensed (Baseline, Week 4 and Week 8), under the supervision of the clinic staff.
  - During priming, continue to press the top of the pump head until product comes out evenly from both of the nozzles. Product that has come out during priming will be discarded.
- Once the pump has been primed and product is coming out from both nozzles evenly, the product is ready for use. Holding the pump at an angle onto the palm of your hand, fully push the pump head until two gels appear from both nozzles: one nozzle will dispense a yellow gel and the other nozzle will dispense a white gel (**Figure 3a**).
- Repeat this one more time (two times total) to get two white and two yellow gels in the palm of your hand (**Figure 3b**). **Figure 3c** shows dispensed product in the palm of your hand. *Note: if only one gel comes out (from one nozzle) or the gels do not come out evenly, please discard and repeat the above steps with two pumps of the head.*
- Carefully blend (mix) the white and yellow gels using 5 to 10 small circular motions with your fingertip or until the colors are blended to give a visually uniform color (gel should now all be one color – off-white/pale-yellow) (**Figure 4a, 4b**).
- Once blended, use one finger to apply a dot (or dab) of the product onto six areas of your face (chin, left cheek, right cheek, nose, left forehead, right forehead) as demonstrated in **Figure 5**.
- You should now have 6 dots (or dabs) of product applied to 6 areas of your face. After applying the product this way, spread the gel over your face and gently rub it in (using any remaining gel left on your palm). It is important to spread the gel over your entire face.
- Wash your hands with soap and water after applying product to your face and put the cap back on the pump. *Note: if there is some product remaining on or around the nozzles, wipe clean with a tissue before replacing the cap.
- A thin layer of study drug should be applied once daily at home (in the evening) to the entire face for twelve weeks (up to the evening prior to the Week 12 visit). Do NOT treat only specific lesions, and do not apply more than the prescribed amount.

Figure 3a

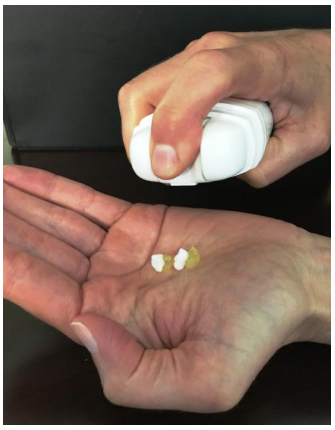

Figure 3b

Figure 3a: One yellow gel and one white gel dispensed from the nozzle after one pump
Figure 3b: Two yellow and two white gels dispensed from nozzle after two pumps (dispensing complete)

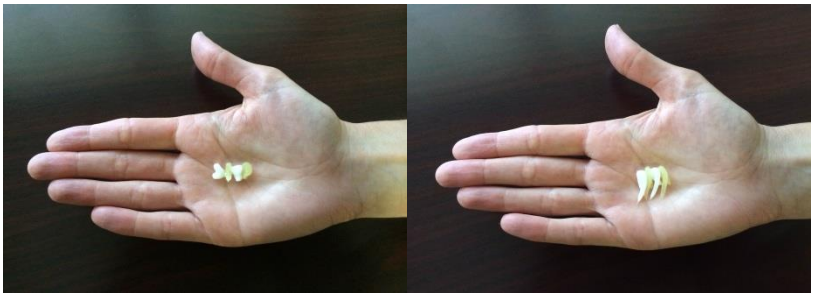

Figure 3c: Visual representation of how the product may look in the palm of your hand. Either option is acceptable.

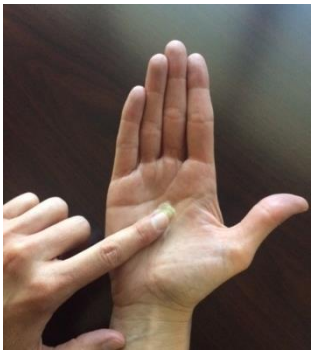

Figure 4a

Figure 4b

Figure 4a: Mix the gels in circular motions with your finger
Figure 4b: Product after mixing in the palm of your hand

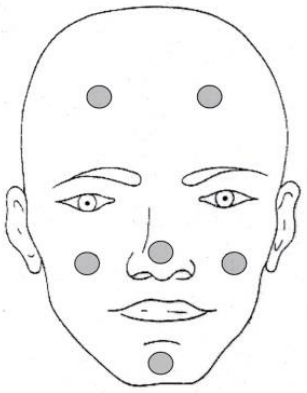

Figure 5: Diagram of application method

Reminders:

- On study visit days (Weeks 2, 4, 8 and 12) please do NOT apply the study drug prior to your on-site study visit.
- On study visit days (Baseline, Weeks 2, 4, and 8) since study drug is applied at the investigational site, please do not re-apply again in the evening.
- Last dose of study drug is applied on the evening prior to the Week 12 visit
- Avoid contact with the eyes, inside the nose, mouth and all mucous membranes.
- Avoid product coming into contact with hair and/or colored fabric, as it may bleach.
- Do not cover the affected areas with any type of dressing, such as gauze.
- THE TEST MATERIAL SHOULD BE USED ONLY BY THE PERSON FOR WHOM IT WAS PRESCRIBED and it should be kept out of the reach of others of limited capacity to read or understand.
- Store at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions (ranges) permitted between 15°C to 30°C (59°F to 86°F). Do not refrigerate. Avoid excessive heat or cold.
- Pumps of test material (including cap) must be returned to the study facility, even if they are empty or damaged.
- If you lose or misplace the pump cap, please contact your study doctor/staff for a replacement.
- If you miss any doses, at your next visit inform the study doctor of the date(s) of the missed dose(s) and ensure it is captured on your study diary.
- 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. Use of study doctor approved sunscreen with at least SPF 15 and wearing protective clothing during the day (e.g., hat) is recommended if you have to be in the sunlight.
- It is important that you inform the study site about any medications (i.e., prescriptions, over-the-counter medications, street drugs, or herbal medications) that you have taken during the study.

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

17.2 Cleansers, Moisturizers and Sunscreen Use Guidelines

Subjects may use the following products as examples of approved products. The Investigator may use his/her 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 eCRF.

Approved Cleanser Examples:

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

Approved Moisturizer Examples:

- CeraVe Cream or Gel
- Moisturel cream or gel
- Nutraderm
- Cetaphil gel or cream
- DML
- Eucerin gel or cream
- Purpose

Approved Moisturizer/Sunscreen Combination Product Examples:

- CeraVe Gel A.M.
- Olay Complete (SPF 15)
- Neutrogena Health Defense Daily Moisturizer (SPF 30)
- Cetaphil Daily Facial Moisturizer (SPF 15)

Approved Sunscreen Examples:

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