NCT#: NCT02965456

CLINICAL STUDY PROTOCOL

IDP-121

Protocol V01-121A-302

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris

Development Phase:	3
Study Design:	Multi-center, randomized, double-blind, vehicle-controlled efficacy and safety study
Date:	04 June 2015
Sponsor:	Dow Pharmaceutical Sciences, a Division of Valeant Pharmaceuticals North America, LLC 1330 Redwood Way Petaluma, CA 94954 [redacted]

CONFIDENTIAL

Nothing herein is to be disclosed without prior approval of the sponsor.

VALEANT
Research & Development

Protocol Review and Approvals

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris

Reviewed and approved:

[redacted]

26/June/2015
Date

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Valeant Pharmaceuticals North America, LLC

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Date

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Valeant Pharmaceuticals North America, LLC

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Date

[redacted]
Valeant Pharmaceuticals North America, LLC

Personnel Responsible for Conducting the Study

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris

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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-121 Lotion

Name of Active Ingredients: Tretinoin 0.05% lotion

Title of Study: A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 Lotion and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris

Number of clinical centers: Multicenter, approximately 32-50 investigational centers in North America

Objective:

The primary objective of this study is to compare the efficacy, safety and tolerability of IDP-121 Lotion and vehicle in the treatment of subjects with acne vulgaris.

Methodology:

This is a multicenter, randomized, double-blind, parallel group, vehicle-controlled, 12-week study to evaluate relative changes in inflammatory and non-inflammatory lesion counts, as well as treatment success using an Evaluator's Global Severity Scale (EGSS) in subjects with moderate to severe acne. Subjects must be at least 9 years of age and older with moderate to severe acne vulgaris (a score of 3 or 4 [moderate to severe] on the EGSS scale), presenting with 20-40 inflammatory facial lesions (papules, pustules, and nodules), 20-100 non-inflammatory facial lesions (open and closed comedones), and ≤ 2 facial nodules.

Approximately eight hundred (800) subjects will be randomized to the following treatment groups:

- 400 Subjects to IDP-121 Lotion, once-daily application
- 400 Subjects to IDP-121 Vehicle Lotion, once-daily application

All subjects will receive once daily, topically-applied treatment to the face for 12 weeks. Subject visits include Screening, Baseline, Week 4, Week 8, and Week 12, at which safety and efficacy assessments will be conducted.

Number of subjects planned:

Approximately 800 subjects will be randomized to the following treatment groups:

- 400 Subjects to IDP-121 Lotion, once-daily application
- 400 Subjects to IDP-121 Vehicle Lotion, 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 screening and baseline visit;
4. Subjects with facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 20 but no more than 40;
5. Subjects with facial acne non-inflammatory lesion (open and closed comedones) count no less than 20 but no more than 100;
6. Subjects with two or fewer facial nodules;

7. Women of childbearing potential and females that 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 or abstinence.) Females on birth control pills must have taken the same type pill for at least three months prior to entering the study and must not change type during the study. Those who have used birth control pills in the past must have discontinued usage at least 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 women 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 2). If the subject wears makeup they must agree to use non-comedogenic makeup.

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;
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 estrogens (eg, Depogen, Depo-Testadiol, Gynogen, Valergen, etc) for less than 12 weeks immediately preceding study entry; Subjects treated with estrogens 12 or more consecutive weeks immediately prior to study entry need not be excluded unless the Subject expects to change dose, drug or discontinue estrogen use during the study;
10. If female, subject has a history of hirsutism, polycystic ovarian disease or clinically significant menstrual irregularities;
11. Treatment of any type of cancer within the last 6 months;
12. Subject uses medications and/or vitamins during the study which are reported to exacerbate acne (azothiaprim, haloperidol, Vitamin D, Vitamin B12, halogens such as iodides or bromides, lithium, systemic or mid-to super-high potency corticosteroids, phenytoin and phenobarbital); Daily vitamins at the prescribed amounts 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;
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 that have not undergone the specified washout period(s) for the following topical preparations used on the face or subjects who require the concurrent use of any of the following topical agents in the treatment area:

Topical astringents and abrasives on face	1 week
Antibiotics on the facial area	2 weeks
Non-allowed moisturizers or sunscreens on face	2 weeks
Other topical anti-acne drugs on face	2 weeks
Soaps containing antimicrobials on the face	2 weeks
Anti-inflammatory agents and corticosteroids on the facial area	4 weeks
Retinoids, including retinol on the face	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 and must be noted in source documents and eCRF.

16. Subjects that 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-121 (tretinoin 0.05%) Lotion, applied topically to the face, once daily for 12 weeks.

Comparator Product: IDP-121 Vehicle Lotion, 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-121 Lotion versus IDP-121 Vehicle Lotion

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) Percent 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 variables:

Mean percent change in inflammatory and non-inflammatory lesion counts from baseline as well as proportion of subjects with at least a two grade improvement in the Evaluator's Global Severity Score from baseline will be evaluated at Weeks 4, 8 and 12.

Efficacy Measurements:

Lesion Counts

At each visit the Evaluator will count the total number of inflammatory lesions (papules, pustules, and nodules) on the subject's face. Nodules will be counted separately but will be included in the total inflammatory lesion count. At baseline, eligible subjects may have no more than 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 – a small, solid elevation less than 5 mm in diameter. Most of the lesion is above the surface of the skin.

Pustule – a small, circumscribed elevation less than 5 mm in diameter that contains yellow-white exudate.

Nodule – a subcutaneous lesion greater than or equal to 5 mm in diameter

Non-inflammatory lesions are defined as follows:

Open comedones (black head) - a lesion in which the follicle opening is widely dilated with the contents protruding out onto the surface of the skin.

Closed comedones (white head)– a lesion in which the follicle opening is closed, but the sebaceous gland is enlarged by the pressure of the sebum build up, which in turn causes the skin around the follicle to thin and become elevated 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

Cutaneous safety and tolerability will be evaluated by tabulations of adverse events and Cutaneous Safety and Tolerability Evaluation scores (scaling, erythema, 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 and erythema (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 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. Finally, the absolute change in lesion count will 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.

The co-primary analysis of the dichotomized EGSS will be based on the logistic regression test stratified by analysis center.

Populations Analyzed and Treatment Groups:

Inflammatory and non-inflammatory lesion counts will be recorded for each Subject at Baseline and at Weeks 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 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 4, 8, and 12 is at least 2 grades less than baseline and Clear or Almost Clear.

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

The safety population will be comprised of all randomized subjects who are presumed to have used the study medication at least once and who provide at least one post-baseline evaluation. A per-protocol (PP) analysis will also be conducted. Subjects will be eligible for the PP analysis if they complete the 12-week evaluation without noteworthy study protocol violations (i.e., any Subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). The PP population will include subjects in the ITT population who do not meet any of the following criteria:

- Failed any of the inclusion/exclusion criteria;
- Have taken any interfering concomitant medications;
- Did not attend the Week 12 visit, with the exception of a discontinuation from the study due to an adverse event related to study treatment or documented lack of treatment effect;
- Missed both the week 4 and week 8 visits;
- 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

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 eight hundred (800) subjects will be randomized to the following treatment groups:

- 400 Subjects to IDP-121 Lotion, once-daily application
- 400 Subjects to IDP-121 Vehicle Lotion, once-daily application

Efficacy:

Primary:

Co-primary efficacy analyses of the absolute change in inflammatory and in non-inflammatory lesions will be conducted on the ITT population. The pre-specified time point will be Week 12. Descriptive statistics will be presented by treatment group for inflammatory and for non-inflammatory lesions as well as the absolute change in inflammatory and in non-inflammatory lesions. All of the testing relating to the analysis of inflammatory and non-inflammatory lesions will use the methods introduced in Section 12.

The co-primary analysis of the dichotomized EGSS (success being at least a 2 grade improvement and achieving Clear or Almost Clear) for the ITT population will be based on the logistic regression test stratified by analysis center.

Secondary:

Mean percent change in inflammatory and non-inflammatory lesion counts from baseline, as well as proportion of subjects with at least a two grade improvement in the Evaluator's Global Severity Score from baseline, will be evaluated at Weeks 4, 8 and 12.

Safety Evaluation:

All subjects who receive medication and provide at least one post-baseline evaluation will constitute the safety population.

Safety will be evaluated by tabulations of adverse events (AEs), Cutaneous Tolerability Evaluations. Cutaneous Safety Evaluation scores (erythema and scaling) and Tolerability (itching, burning, and stinging) will be presented with descriptive statistics at Baseline and at Weeks 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 and an abbreviated physical exam will be conducted on all subjects at specified visits. For females of child-bearing potential (FOCBP), urine pregnancy testing and serum pregnancy testing will occur at specified visits.

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 medication, the action taken regarding study medication 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 medication. 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 proportion 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 medication.

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

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

Subject Self-Assessments

An exploratory patient self assessment questionnaire and satisfaction survey will also be administered during the study.

Subjects will be asked to complete three questionnaires during the study: the Subject Self Assessment scale, the Patient Satisfaction Survey and the Acne-Specific Quality of Life Questionnaire. The Investigator assessments (EGSS, lesion counts) will be conducted independently of these subject self assessments. The EGSS should always be completed prior to the lesion counts. Inferential statistical analysis will not be performed on these questionnaires; 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
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
cGCP	Current Good Clinical Pratice
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
IATL	Investigator's Assessment of Total Lesions
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Affairs
mL	Milliliter
OTC	Over-the-counter
PP	Per protocol
PSS	Patient Satisfaction Survey
QoL	Quality of Life
SAE	Serious adverse event
SSA	Subject Self Assessment
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 (all-trans-retinoic-acid) is a member of the retinoid family of compounds and is a metabolite of Vitamin A that occurs naturally in animal and human tissues. While oral retinoids (eg, isotretinoin) are reserved for treatment of severe nodular acne or severe acne resistant to oral antibiotics, topical retinoids (eg, tretinoin or isotretinoin) applied daily are used to inhibit the formation of comedones and usually clear even severe comedonal acne within a few months [6]. Topical formations of tretinoin have been used to treat acne in the United States (US) and the European Union for more than 25 years.

Tretinoin binds with high affinity to specific retinoic acid receptors located in both the cytosol and nucleus, but cutaneous levels of tretinoin in excess of physiologic concentrations occur following application of a tretinoin-containing topical drug product. Tretinoin activates 3 members of the retinoid acid (RAR) nuclear receptors (RARα, RARβ, and RARγ) which act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation; however, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms, or both. Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

IDP-121 is a lotion containing 0.05% tretinoin for the topical treatment of acne. This proposed product is the first lotion formulation developed for tretinoin and will be evaluated for effectiveness in treating acne vulgaris.

6 Study Objectives and Purpose

The objective of the study is to evaluate the efficacy, safety and tolerability of a once-daily topical application of IDP-121 Lotion compared to its vehicle (IDP-121 Vehicle Lotion) in subjects with moderate to severe acne vulgaris (a score of 3 or 4 [moderate to severe] on the EGSS scale).

7 Investigational plan

7.1 Overall Study Design and Plan: Description

This is a multicenter, randomized, double-blind, parallel-group study designed to assess the safety, efficacy and tolerability of IDP-121 Lotion in comparison with its vehicle. 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 800 subjects will be enrolled into this study and randomized into one (1) of two (2) treatment groups: 400 subjects in the IDP-121 Lotion, once daily application group,

and 400 subjects in the IDP-121 Lotion Vehicle, once daily application group. Subjects will be enrolled at a minimum of 32 and maximum of 50 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 4, 8, and 12).

An interactive web based response system (IWRS) will be employed to facilitate randomization of study patients. Treatment assignments and study drug kit numbers will be generated centrally by the IWR system. 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 for 12 weeks. The initial application will be made 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. Subjects will apply their daily treatments at home as explained by the study coordinator or designee at each investigational center. During post-baseline study visits (Weeks 4, 8 and 12) the subjects will be asked to return their used tubes of study drug and will be dispensed new tubes of study drug (only Weeks 4 and 8; 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 three questionnaires during the study: the Subject Self Assessment scale (SSA, Appendix 17.3), the Patient Satisfaction Survey (PSS, Appendix 17.4) and the Acne-Specific Quality of Life Questionnaire (Acne-QoL, Appendix 17.5). The Investigator assessments (EGSS, lesion counts) will be conducted independently of these subject self assessments. The EGSS should be completed prior to the lesion counts. Subjects will assess the severity of their acne at the baseline visit and at Weeks 2 (at home), 4, 8, and 12 by completing the SSA. The Week 2 SSA form will be dispensed to the subject at the baseline visit with instructions to complete it two weeks later and return it the Week 4 visit; sites should call the Subject at Week 2 to remind them to complete the SSA. Subjects will complete the PSS related to prior therapy at baseline, and at Week 12 will complete the PSS related to current study medication. The Acne-QOL will be completed at baseline and Week 12. Inferential statistical analysis will not be performed on these questionnaires; the subjective responses will be compared between treatment groups for trends.

Information on reported and observed adverse events (AEs) will be obtained at each visit. An abbreviated physical examination will be performed at Baseline and Week 12 (end of treatment, final visit) for all subjects.

For all female subjects of childbearing potential, urine pregnancy testing will be performed at Screening and confirmed at Baseline with a urine pregnancy test prior to randomization, and at Weeks 4, 8 and 12. Serum pregnancy tests will also be conducted at Screening and Week 12.

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.

Table 1. Study Design and Schedule of Assessments

PROCEDURES	VISIT 1[1] Screening Visit	VISIT 2[2] Baseline Day 0	VISIT 3[2] Week 4 (Day 28 ±3 days)	VISIT 4[2] Week 8 (Day 56 ± 3 days)	VISIT 5[2,3] Week 12 (Day 84 -3/+5 days)
Informed consent/Assent	X				
Obtain Subject Number from IWRS	X				
Demographics	X				
Medical history	X	X			
Inclusion/Exclusion criteria	X	X			
Previous therapies	X				
PSS & Acne-QoL		X			X
SSA[4]		X	X	X	X
Urine Pregnancy Test (UPT) (FOCBP)	X	X	X	X	X
Serum Pregnancy Test (FOCBP)	X				X
Abbreviated physical examination		X			X
Oily/shiny skin assessment		X			X
Lesion Counts	X	X	X	X	X
EGSS	X	X	X	X	X
Photographs (select sites only)		X			X
Cutaneous Safety Evaluation		X	X	X	X
Tolerability Evaluation		X	X	X	X
Randomization in IWRS (obtain kit #)		X	X	X	
Administer Subject Instructions (Appendix 17.1)		X			
Dispense Study Drug[5]		X	X	X	
Weigh Study Drug		X	X	X	X
Study Drug applied at investigational center		X			
Study Drug Collected			X	X	X
Subject Diary Calendar dispensed		X	X	X	
Subject Compliance Reviewed / Diary			X	X	X
Adverse Events	X	X	X	X	X
Concomitant Therapy and Prohibited Therapies Review	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] All visit dates are in reference to baseline, e.g., Visit 4 occurs 8 weeks +/- 3 days after baseline visit.
[3] All Week 12 procedures should be completed for all subjects who terminate early.
[4] The Week 2 SSA will be sent home with the subject during the baseline visit (Visit 2) with instructions to complete it at two weeks and return it at the Week 4 visit. The site should call the subject at Week 2 to remind them to take the Week 2 SSA.
[5] Dispense one tube of test material at the Baseline, Week 4 and Week 8 visits.

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 assessment at the screening and baseline visit;
4. Subjects with facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 20 but no more than 40;
5. Subjects with facial acne non-inflammatory lesion (open and closed comedones) count no less than 20 but no more than 100;
6. Subjects with two or fewer facial nodules;
7. Females of childbearing potential[1] and females that 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 or abstinence.) Females on birth control pills must have taken the same type pill for at least three months prior to entering the study and must not change type during the study. Those who have used birth control pills in the past must have discontinued usage at least 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 medication. Kits will be provided by the CRO.

moisturizer/sunscreen combination products (see Appendix 2). If the subject wears makeup they must agree to use non-comedogenic makeup.

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;
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 estrogens (eg, Depogen, Depo-Testadiol, Gynogen, Valergen, etc) for less than 12 weeks immediately preceding study entry; Subjects treated with estrogens 12 or more consecutive weeks immediately prior to study entry need not be excluded unless the Subject expects to change dose, drug or discontinue estrogen use during the study;
10. If female, subject has a history of hirsutism, polycystic ovarian disease or clinically significant menstrual irregularities;
11. Treatment of any type of cancer within the last 6 months;
12. Subject uses medications and/or vitamins during the study which are reported to exacerbate acne (azothiaprim, haloperidol, Vitamin D, Vitamin B12, halogens such as iodides or bromides, lithium, systemic or mid-to super-high potency corticosteroids, phenytoin and phenobarbital); Daily vitamins 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;
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 that have not undergone the specified washout period(s) for the following topical preparations used on the face or subjects who require the concurrent use of any of the following topical agents in the treatment area :

Topical astringents and abrasives on face	1 week
Antibiotics on the facial area	2 weeks
Non-allowed moisturizers or sunscreens on face	2 weeks
Other topical anti-acne drugs on face	2 weeks
Soaps containing antimicrobials on the face	2 weeks
Anti-inflammatory agents and corticosteroids on the facial area	4 weeks
Retinoids, including retinol on the face	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 and must be noted in source documents and eCRF.

16. Subjects that 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 (eg, severe adverse reactions), or at the subject's request.
- When the requirements of the protocol are not followed.
- When a concomitant therapy likely to interfere with the results of the study is reported, or required by the subject (the investigators will report all such information

on the source documents/case report forms (CRFs) and decide, in accordance with the sponsor, whether the subject is to be withdrawn).

- When a subject is lost to follow-up. The investigators will try twice to reach the subject by telephone and will send a follow-up letter by certified mail before considering that the subject is lost to follow-up. These actions will be reported on the End of Study CRF 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 the final CRF, and, if need be, on the AE form. In any case, no subject who has been included and has a study 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 2 phone calls and a certified letter.

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

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

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

Withdrawal by Parent/Guardian – An indication that the study participant has been removed from the study by the parent or legal guardian. 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 CRF.

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 study drug groups in a ratio of 1:1 (IDP-121 [tretinoin 0.05%] Lotion : IDP-121 Vehicle Lotion). 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 (eg, 101001, 101002). The study drug kit will be assigned to subjects based on a randomization code and kit will be dispensed to the subjects at Baseline by the IRW system, and at 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 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 tubes as scheduled.

9.3 Un-blinding

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. The investigator will record the code break in the subject's source documents.

9.4 Prior and Prohibited Concomitant Medication or Therapy

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

Topical astringents and abrasives on the face	1 week
Antibiotics on the facial area	2 weeks
Non-allowed moisturizers or sunscreens on the face	2 weeks
Other topical anti-acne drugs on the face	2 weeks
Soaps containing antimicrobials on the face	2 weeks
Anti-inflammatory agents and corticosteroids on the facial area	4 weeks
Retinoids, including retinol on the face	4 weeks

If the subject requires topical treatment for acne on areas other than the face (eg, chest or back), the investigator may prescribe a product that does not contain tretinoin and noted in 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 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 treatment (except as noted above) other than the study drug will be permitted for acne.

Information on concomitant 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 (eg, aspirin, Tylenol, birth control pills, vitamins, moisturizers, sunscreens). Every attempt should be made to keep concomitant therapy dosing constant during the study. Any change to concomitant therapy should be noted on the Concomitant Therapy source document and eCRF.

All cleansers and moisturizers and other topical products used on the treatment area that are not prescription products will be captured on the Other Skin Care Products source document and eCRF. Subjects must use Investigator approved cleansers and moisturizers.

Subjects should avoid excessive UV exposure by such activities as sun bathing or tanning booths.

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 tubes dispensed at each treatment visit to the next subsequent study visit. Each tube will be weighed 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 CRF. The subject will also be sent home with a Subject Self Assessment (SSA) survey at the Baseline visit, with instructions to complete it at home at two (2) weeks after their baseline visit, and return it at the Week 4 study visit.

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 patients or a small group of patients 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 patient, when the patient or investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria) and the patient was enrolled without prior sponsor approval, or when there is nonadherence to FDA regulations and/or ICH GCP guideline.

The investigator or designee must document and explain in the patients' 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 patients 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-121 Lotion and IDP-121 Vehicle Lotion

Chemical structure and formula for the active ingredients in IDP-121 Lotion and vehicle are listed in the tables below:

Table 2. Drug Substances Identification

Active Ingredient	Tretinoin 0.05%
Chemical Name	(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenoic acid
Chemical Class	Retinoid
Molecular Formula	$C_{20}H_{28}O_2$
CAS Registry Number	302-79-4

Table 3. Test Product Identification

	Investigational Product	Vehicle
Name of Active Ingredient	Tretinoin, EP / USP	N/A
Drug Name/Formulation/ Concentration	IDP-121 Lotion [Tretinoin 0.05%]	IDP-121 Vehicle Lotion
Manufacturer	Valeant Pharmaceuticals International, Inc. 2150 St. Elzear Boulevard West Laval (Quebec), Canada H7L 4A8	
Packaging	45 g tube	45 g tube
Storage Requirements	Store at 20°C to 25°C (68°F to 77°F)	Store at 20°C to 25°C (68°F to 77°F)
Appearance	Opaque pale yellow lotion	Opaque pale yellow lotion
Dosing Schedule	Once daily x 12 weeks	Once daily x 12 weeks
Route of Administration	Topical Application	Topical Application

10.1.1 Packaging and Labeling

IDP-121 Lotion and its vehicle 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 IWRS specific kit number will be assigned to be used for that randomized subject by the IWR system. Each subject kit will contain one tube, which has 45 grams of study material. A new subject kit will be assigned to a subject at each visit: Baseline, Week 4 and Week 8. The subjects will be dispensed one kit at Baseline as assigned in the IWR system. The tube will be

weighed prior to dispensing. The subject will bring the tube to the next study visit (Week 4), where it will be collected and weighed; one new tube will be dispensed again by the IWR system at Week 4, weighed and provided to the subject. The same will occur at the Week 8 visit.. If the subject loses a tube (lost or damaged tube), another kit will be dispensed via IWRS. Each tube dispensing will be documented on the drug accountability log.

Each subject kit (and tube) will have a single panel label. Labels will contain the following information:

- Protocol Number
- Kit Number
- Contents
- Space for entry of the subject initials
- Space for entry of date dispensed
- The sponsor name, Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals N.A., LLC
- The quantity of product (45 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

Test material will be applied topically to the face once a day for a period of 12 weeks. Test material will be applied as a thin coating (a dab the size of a large pea) that is gently rubbed in to the skin. The test material use should 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 the test material at approximately the

same time every day for 12 weeks after cleansing. On study visit days subjects should be instructed to wait until after their study visit to apply study medication. No time interval between dosing and meals or any other activity is specified. Subjects will be instructed to gently wash their face with a Sponsor approved 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 tube to dispense a pea-sized amount of study drug to their fingertip. This dose should then be dotted on to 6 areas (chin, left cheek, right cheek, nose, left forehead, right forehead) on the face. After distributing the dose in this manner the subject should gently rub the lotion 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.

The subjects will be instructed to continue using the same Sponsor approved facial cleanser and moisturizer 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 store the test material at room temperature.

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. Tubes will be weighed (with the cap on) before dispensing to and upon return by the subjects, and weights will be recorded on the pharmacy log and appropriate CRF. All used and unused supplies will be returned to sponsor/designee for destruction at the conclusion of the study.

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

The following procedures will be conducted at this visit:

1. Obtain written informed consent prior to performing any study procedures. Subjects less than 18 years of age 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 your site) and the 3-digit chronological order screening number, assigned by the IWR system and starting with 101 (eg, 101 001, 101 002, 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 Assessment followed by inflammatory lesion count and non-inflammatory lesion count to determine eligibility.
7. Perform a Urine Pregnancy Test and Serum Pregnancy Test for all females that are pre-menses and females of childbearing potential. The urine pregnancy tests will be supplied by the CRO.
8. Discuss allowed 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. Verify that the subject meets the applicable inclusion/exclusion criteria as outlined in Sections 8.1 and 8.2.
11. Remind subject to not apply test medication on day of next study visit prior to the clinic visit.

12. If the subject requires a washout, schedule the Baseline visit to occur after the washout is complete. If no washout is required, the Screening and Baseline visits may occur on the same day.
13. Schedule subject to return for the Baseline/Day 0 visit. If the subject requires a washout, schedule the Baseline/Day 0 visit to occur after the washout is complete.

NOTE: At the Screening and Week 12 visits, serum pregnancy testing is **mandatory** for all females of childbearing potential. In addition, a urine pregnancy test must be completed at Screening and at the Baseline visit prior to randomization, and at Weeks 4, 8 and 12. The decision may be made by the investigator to do additional pregnancy tests during the course of the study.

11.1.2 Visit 2: Baseline Visit (Day 0)

If a washout is not needed, this visit may occur on the same day as the Screening Visit (Visit 1). If a washout is needed, Visit 2 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 Subject Self Assessment (SSA), Patient Satisfaction Survey (PSS) and the Acne-Specific Quality of Life Questionnaire (Acne-QoL) will be completed by the subject and collected prior to any other study-related procedures. The Week 2 SSA will be sent home with the subject with instructions to complete it at two weeks and return it at the Week 4 visit.
2. Verify that the subject continues to meet the applicable inclusion/exclusion criteria as outlined in Sections 8.1 and 8.2.
3. Record changes in any concomitant medications since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant therapies as per Section 9.4.
4. Perform a Urine Pregnancy Test for all females that are pre-menses and females of childbearing potential. The urine pregnancy tests will be supplied by the CRO.
5. Perform an abbreviated physical exam, including measurements of height and weight, and vital signs. Any abnormal physical exam findings will be recorded.
6. The Evaluator will query the subject regarding how oily/shiny their facial skin has been in the past week.
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. Assign the subject the presented kit number (this number will be generated from the Interactive Web Response system, (IWRS)).
10. The study coordinator or designee will weigh the tube within the assigned kit 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.
11. 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.
12. Record any AEs or changes in AEs since the screening visit and/or reported spontaneously by the subject.
13. *Selected Sites only* - Obtain representative photographs of the face.
14. Schedule the next study visit at Week 4 (Day 28 ± 3 days). Remind the subject to not apply test medication on day of next study visit, prior to the clinic visit.

11.1.3 Visit 3 and 4: Week 4 (Day 28 ± 3 Days) and Week 8 (Day 56 ± 3 Days) Visits

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

1. The take-home Week 2 SSA will be collected during the Week 4 study visit.
2. The Week 4 or Week 8 SSA will be conducted and collected.
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 since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant therapies as per Section 9.4.
6. Record any new AEs reported spontaneously by the subject or changes in anyongoing AEs.
7. Perform a Urine Pregnancy Test for all females that are pre-menses and females of childbearing potential. The urine pregnancy tests will be supplied by theCRO.
8. The study drug technician will retrieve and weigh the used test material tube and assign the subject another kit number (this number will be generated from the Interactive Web Response system, (IWRS) and dispense a new subject kit of test material. The tube will be weighed on a calibrated scale. Record the weight to the nearest 0.1 gram.

9. 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.
10. Schedule the subsequent study visit, as applicable. Remind the subject to not apply test medication on the day of the next study visit, prior to the clinic visit.

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

The following procedures will be conducted at this visit:

1. The Week 12 SSA, PSS and 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 height and weight, and vital signs. Any abnormal physical exam findings will be recorded.
3. The Evaluator will query the subject regarding how oily/shiny their facial skin has been in the past week.
4. 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.
5. The Evaluator will perform Cutaneous Safety and Tolerability Evaluations.
6. Record changes in any concomitant medications since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant therapies as per Section 9.4.
7. Record any new AEs reported spontaneously by the subject or changes in anyongoing AEs.
8. The study diary calendar will be collected and reviewed for compliance. Any missed doses or deviations should be reported.
9. The study drug technician will retrieve all test material tubes from the subject and weigh the tubes on a calibrated scale and record the weight to the nearest 0.1 gram.
10. For women of child bearing potential, collect a blood sample for a serum pregnancy test and perform a final Urine Pregnancy Test for all females that are pre-menses and females of childbearing potential. The urine pregnancy tests will be supplied by the CRO.
11. *Selected Sites only* - Obtain representative photographs of the face.
12. Exit the subject from the study and complete the end of study CRFs.

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, the same Evaluator must 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 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. 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 – a solid, elevated lesion less than 5 mm
Pustule – an elevated lesion containing pus less than 5 mm
Nodule – palpable subcutaneous lesion greater than 5 mm; has depth, not necessarily elevated
Non-inflammatory lesions are defined as follows:

Open comedones (blackhead) – plugged hair follicle with dilated/open orifice; black in color
Closed comedones (whitehead) – plugged hair follicle: small opening at skin surface

11.2.3 Other Assessments

Oily/Shiny Face Assessment

The subject will be asked at Baseline and Week 12 to assess how oily their skin has been in the past week by the scale below:

Oily/Shiny skin assessment
0 – None No oily or shiny skin on face
1 – Mild Mild oily or shiny skin on face
2 – Moderate Definite oily or shiny skin on face
3 – Severe Extremely oily or shiny skin on face

If subject answers 1, 2 or 3 to the above they will also be asked how often the oily skin made them feel bothered during the past week with scale below:
0 – Not bothered at all
1 – A little bothered
2 – Moderately bothered
3 – Very bothered
4 – Extremely bothered

Photography

At select sites, photographs of the face will be taken at Baseline and Week 12, at a minimum. 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 tolerability will be evaluated through assessment of selected local signs and symptoms at the drug-application site: itching, burning and stinging at the time of the visit.

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.

(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

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.

11.3.4 Pregnancy Tests

All female subjects of childbearing potential will undergo serum pregnancy testing at Screening and Week 12. In addition, urine pregnancy testing will be performed at Screening and prior to randomization at Baseline, and at Week 4, 8 and Week 12. The urine pregnancy tests will be supplied by the CRO.

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.

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 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 CRF:

- 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 will be considered an SAE, 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: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required
- Severe: Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible; may be incapacitating or life threatening

11.4.5 Assessment of Causality

The investigator should assess the relationship of the AE, if any, to the study drug as either "Related" or "Not Related". The following should be taken into account when assessing 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 within 24 hours of the investigator's awareness of the event. All SAEs must be reported via confirmed facsimile and 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:

[redacted] Medical Monitor

&

[redacted] Program Manager [TKL Research, Inc.]

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 CRF 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 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 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, 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

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 or Package Insert) 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 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 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 within 24 hours of the investigator's awareness of the pregnancy. All confirmed pregnancies must be reported via confirmed facsimile/email transmission and must be submitted on a SAE form within 24 hours of

the investigator's awareness of the pregnancy using the same reporting as procedure for an SAE under 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. Finally, the absolute change in lesion count will 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.

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 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 4, 8, and 12.

The EGSS will be recorded for each Subject. The EGSS will be dichotomized into "success" and "failure" at Week 4, 8 and 12 with a subject considered a success for those visits if the Global Severity Score is at least 2 grades less than baseline and are Clear or Almost Clear. An additional assessment of subjects who have achieved 2 grade improvement will be also be conducted as a secondary efficacy variable.

The subject will be asked at Baseline and Week 12 to assess how oily their skin has been in the past week.

All assessments will be conducted for both ITT and PP.

12.1 Assessment of Efficacy

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

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
- Proportion of subjects who have a least a 2 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

There are three Week 12 secondary efficacy endpoints:

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

There are three Week 8 secondary efficacy endpoints:

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

There are three Week 4 secondary efficacy endpoints:

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

12.1.3 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 12.1.7. 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.

12.1.4 Statistical Hypothesis Testing and Control of Multiplicity

Statistical hypothesis testing for lesion count analyses will use the statistical model introduced in Section 12.1.3 and employs the methods of Section regarding missing values. The analysis of the dichotomized Evaluator's Global Severity Score will be based on the logistic regression test stratified by analysis center and employs the methods of Section 12.1.7 regarding missing values.

The overall Type I error will be controlled by requiring the co-primary efficacy endpoints of each group 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	Percent change in non-inflammatory lesion count from baseline to Week 8
4	Percent change in inflammatory lesion count from baseline to Week 8
5	Percent change in non-inflammatory lesion count from baseline to Week 4
6	Percent change in inflammatory lesion count from baseline to Week 4
7	Proportion of subjects who have a least a 2 grade reduction at Week 12 from baseline in the Evaluator's Global Severity Score
8	Proportion of subjects who have a least a 2 grade reduction at Week 8 from baseline in the Evaluator's Global Severity Score
9	Proportion of subjects who have a least a 2 grade reduction at Week 4 from baseline in the Evaluator's Global Severity Score

12.1.5 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 4, 8, and 12.
- Frequency and percent distributions of the dichotomized Evaluator's Global Severity Score at Baseline and Weeks 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 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 4, 8, and 12.
- Frequency and percent distributions for the Oily/Shiny assessments at Week 12

Means, standard deviations and frequency counts (rounded to the nearest whole number) will be computed from the multiply imputed MCMC data for the variable.

12.1.6 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 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. 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 active 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 mail effect will be investigated to determine if the main site-to-site variability is such that it could mask the analysis center effects. Thus, if computationally possible, a one-way ANCOVA (for lesion count variables) or a logistic regression analysis (for EGSS) with a factor of site will be conducted prior to pooling. If the data structure interferes with the logistic regression, a

descriptive analysis of the site effect will be undertaken. Conclusions appropriate to the findings of this step will be presented.

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 and secondary 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. 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.

12.1.7 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 Markov Chain Monte Carlo (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 4 distinct phases with these principal tasks:

1. Calculated the number of missing values to be estimated by MCMC (nmiss) for 12 week value.
2. 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 x nmiss' times to generate '5 x nmiss' data sets. The resulting data sets for each treatment arm will be combined into one complete data set for each imputation.
3. For each complete data set, the absolute change in lesion counts for baseline minus the 12 week value will be computed. Each complete data set will be analyzed as specified for the particular analysis.
4. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

EGSS Missing Data Imputation

A similar procedure will be used for the analyses based on proportion of EGSS successes wherein the ANCOVA analysis is replaced with a logistic regression analysis. Specifically, missing 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 4 principal tasks:

1. Calculate the number of missing values to be estimated by MCMC (nmiss) for 12 week value.
2. Create a data set, one for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing EGSS values in each data set will be filled in using the MCMC method '5 x nmiss' times to generate '5 x nmiss' data sets. The resulting data sets for each treatment arm will be combined into one complete data set by imputation.
3. For each complete data set, the dichotomous success rate (clear or almost clear with a 2-point change from baseline) will be computed. The 12-week estimated global 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.

12.1.8 Sensitivity Efficacy Analyses

Sensitivity analyses for absolute change in lesion count

The first sensitivity analysis for absolute change in lesion count 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. Multiple imputation will involve 4 principal tasks:

1. Calculate the number of missing values (nmiss) for absolute change in lesion count.
2. Missing values will be filled in '5 x nmiss' times to generate '5 x nmiss' complete 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-parameteric method.

3. 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.
4. Results from these analyses will be combined into a single inference.

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. Multiple imputation will involve 4 principal tasks:

1. Calculate the number of missing values (nmiss) for absolute change in lesion count.
2. Missing values will be filled in '5 x nmiss' times to generate '5 x nmiss' complete 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).
3. Each complete data set will be analyzed with a logistic regression a factors of treatment group and analysis center.
4. Results from these analyses will be combined into a single inference.

12.1.9 Subgroup Analyses

Subset analyses will be conducted for the ITT populations for the subgroups 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 be include with categories of less than 18, 18 to less than the median age and greater than or equal to the median age. 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.

12.2 Assessment of Safety

Safety will be evaluated by tabulations of adverse events (AEs), Cutaneous Safety Evaluation, and Tolerability Evaluations. Cutaneous Safety Evaluation scores (erythema and scaling) and Tolerability (itching, burning, and stinging) will be presented with descriptive statistics at Baseline and at Weeks 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 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 medication, the action taken regarding study medication usage, the action taken regarding 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, severity, seriousness, and relationship to study medication. 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 medication. 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 proportion 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 medication.

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 Vital Sign Measurements

Changes from Baseline in vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits.

12.2.3 Concomitant Medications

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

12.2.4 Subject Self-Assessments

Subjects will be asked to complete three questionnaires during the study: the Subject Self Assessment scale, the Patient Satisfaction Survey and the Acne-Specific Quality of Life Questionnaire (Appendices 17.3, 17.4 and 17.5). Descriptive statistics will be used to summarize the data reported for each questionnaire. No Inferential analyses will be conducted.

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 both the ITT population and the PP population. 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 not be compared statistically.

12.5 Protocol Deviations

All protocol deviations will be reported to the sponsor and recorded throughout the study. A tabulation of protocol deviations will be included in the final study report.

12.6 Compliance

No formal evaluations of compliance are planned.

12.7 Interim Analyses

No interim analyses are planned.

12.8 Additional Statistical Considerations

12.8.1 Analysis Populations

Approximately 800 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:

- 400 subjects will be randomized to receive IDP-121 Lotion, once daily application
- 400 subjects will be randomized to receive IDP-121 Vehicle Lotion, once daily application

The ITT population will consist of all randomized subjects who received study medication. The safety population will be comprised of all randomized subjects who are presumed to have used the study medication at least once and who provide at least one post-baseline evaluation.

An intent-to-treat (ITT) analysis will be conducted on all study subjects. 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, with the exception of a discontinuation from the study due to an adverse event related to study treatment or documented lack of treatment effect;
- Missed both the week 4 and week 8 visits;
- 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.

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.

The safety population will be comprised of all randomized subjects who are presumed to have used the study medication at least once and who provide at least one post-baseline evaluation.

12.8.2 Sample Size Determination

These power calculations are based primarily on the observed Week 12 results of the Study 2 in Atralin™ (tretinoin) Gel, 0.05% NDA 022070 application. This study was a two-arm trial of Atralin™ versus its vehicle and is felt to be a relevant study in NDA 022070 for powering the current study. The next three power calculations are constructed from the results of Study2.

A sample size of 400 per treatment arm has at least 96% power to detect a statistically significant difference with a significance level of 0.05. The estimated absolute change from baseline in

treatment means were 6.5 and 3.5 for Atralin™ versus its vehicle, respectively, with a standard deviation of 11.3.

A sample size of 400 per treatment arm has greater than 99% power to detect a statistically significant difference with a significance level of 0.05 using the estimated absolute change from baseline in treatment means of 17.8 and 9.9 for Atralin™ versus its vehicle, respectively, with a standard deviation of 24.7.

The sample size estimates for the dichotomized EGSS require a substantially larger enrollment in order to achieve a power of at least 90%. The success rates observed in the second Atralin™ study was 23% for Atralin™ and 14% for its vehicle which is a difference of 9%. Approximately 90% power is achieved with sample sizes of 400 per treatment group, respectively, using a 1:1 randomization.

It is noted that the same differential in success rates was observed in Study 1 (Atralin™ (tretinoin) Gel, 0.05% NDA 022070 application). The success rates observed in the first Atralin™ study was 13% for Atralin™ and 4% for its vehicle which is also a difference of 9%. Using these estimates, more than 99% percent power is achieved with sample sizes of 400 per treatment group.

The clinical study will be conducted under a common protocol at each investigational site and every effort will be made to promote consistency in study execution at each investigational site as well as uniform evaluation of the EGSS evaluation for subjects at the various study visits. The experience in clinical trial execution gained during the execution of several acne studies conducted under the guidance of the Sponsor raises the expectation that the differential between the success rates of the two arms will be greater than 9%. Thus, the power of the EGSS is expected to be at least 95% for sample sizes of 400 subjects in each arm.

Individually and collectively the considerations lead to a choice of randomizing 400 subjects per treatment group.

12.8.3 Handling of Missing Data

The method of multiple imputation will be used (see Section 12.1.7).

12.8.4 Multicenter Issues

The study will be conducted at multiple investigational centers in North America with the intention of pooling the results for analysis.

12.8.5 Multiplicity Issues

Not applicable.

12.8.6 Windowing Rules

The timing of all study visits is relative to Baseline (Day 0). The 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, the role of the study technician, 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 CRFs. The investigator or designee will enter the information required by the protocol into the source documents and CRFs provided by the sponsor or designee. Subjects will be identified in the CRFs by their assigned subject number and initials only.

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

14 Ethics and Administrative Issues

14.1 Ethical Conduct of the Study

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

14.2 Ethics Review

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. 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 (ie, 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 (eg, laboratory tests). All required data should be recorded in the study documentation completely for prompt data review. Upon study completion or at any other time specified by the sponsor or designee, the appropriate study documents must be submitted.

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

- A statement indicating that the subject has been enrolled in the study and the subject number
- Date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (eg, medical history, screening evaluations)

- Dates of all study related visits and results of any evaluations/procedures performed, including who performed each assessment at each visit
- Use of any concurrent medications during the study
- Documentation of study drug accountability
- Any and all side effects and AEs must be thoroughly documented to conclusion
- Results of any diagnostic tests conducted during the study
- The date the subject exited the study and a statement indicating that the subject completed the study or was discontinued early, including the reason for discontinuation

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

15.2 Retention of Records

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

The investigator will allow representatives of the sponsor's monitoring team, the governing IRB/IEC, the FDA, and other applicable regulatory agencies to inspect all study records, CRFs, 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 CRF, and compliance with FDA or other regulatory agency regulations.

16 References

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8. Orfanos CE, Ehlert R, Gollnick H. The retinoids. A review of their clinical pharmacology and therapeutic use. Drugs. 1987;34(4):459-503.

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17 Appendices

17.1 Subject Instruction Sheet

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

A thin coating of test material should be applied once daily (about the same time every day) to the entire face for twelve weeks. Use the tube to dispense a pea-sized amount of study drug to your fingertip.

This dose should then be dotted on to 6 areas (chin, left cheek, right cheek, nose, left forehead, right forehead) on the face. After distributing the dose in this manner, gently rub the lotion into the skin. This amount should be used to evenly cover the entire face excluding the mouth, eyes and lips. It is important to treat your entire face.

Do NOT treat only specific lesions. DO NOT APPLY MORE THANTHE PRESCRIBED AMOUNT.

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

Reminders:
- On study visit days please wait until after your study visit to apply the study medication.
- Avoid contact with the eyes, inside the nose, mouth and all mucous membranes.
- 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 permitted between 15°C to 30°C (59°F to 86°F). Do not freeze. Avoid excessive heat or cold.
- Tubes of test material must be returned to the study facility, even if they are empty.
- If you miss any doses, at your next visit inform the study doctor of the date(s) of the missed dose(s).
- Continue to use the same, study doctor approved, cleanser, moisturizer and sunscreen throughout the study.
- You must not use any other treatment for your facial acne while you are participating in this study.
- Avoid unnecessary sun exposure and tanning booths.

- It is important that you inform the study site about anymedications (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. The Investigator may use their discretion on what products each subject may use in the treatment area during the study. Subjects may only use Investigator approved products on the treatment area. Information regarding products used should be captured in the source document and recorded on the facial skin care section of the eCRF.

Approved Cleansers:

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

Approved Moisturizers:

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

Approved Moisturizer/Sunscreen Combination Products:

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

Approved Sunscreens:

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

17.3 Subject Self Assessment Scoring Scale

Baseline Subject Question

How would rate the current severity of your facial acne condition on a scale of 1-7?

(Check only one box)

☐ 1, Clear or almost clear skin (>90%);

☐ 2, Moderately clear skin (>80% but ≤ 90%);

☐ 3, Fairly clear skin (>70% but ≤ 80%);

☐ 4, Acne covered about 50% of the face;

☐ 5, Fairly severe acne (>70% but ≤ 80% coverage);

☐ 6, Moderately severe acne (>80% but ≤ 90% coverage);

☐ 7, Severe acne, with almost total coverage (>90%).

Week 2 (at-home), 4, 8, and 12 Subject Question

How would rate the current severity of your facial acne condition on a scale of 1-7?

(Check only one box)

☐ 1, clear (100%);

☐ 2, almost clear (90% to <100%);

☐ 3, marked improvement (75% to <90%);

☐ 4, moderate improvement (50% to <75%);

☐ 5, fair improvement (25% to <50%);

☐ 6, no change;

☐ 7, worse

17.4 Patient Satisfaction Survey (PSS)

Baseline Question

On a scale of 1-10 with 1 being the least satisfied and 10 being the most satisfied please rate your level of satisfaction with your prior facial acne therapy.

_____

Week 12 Question

On a scale of 1-10 with 1 being the least satisfied and 10 being the most satisfied please rate your level of satisfaction with your current facial acne study treatment.

_____

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

1. In the past WEEK, how unattractive did you feel because of your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

2. In the past WEEK, how embarrassed did you feel because of your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

3. In the past WEEK, how self-conscious (uneasy about oneself) did you feel about your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

4. In the past WEEK, how upset were you about having facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

5. In the past WEEK, how annoyed did you feel at having to spend time every day cleaning and treating your face because of your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

6. In the past WEEK, how dissatisfied with your self-appearance did you feel because of your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

7. In the past WEEK, how concerned or worried were you about not looking your best because of your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

8. In the past WEEK, how concerned or worried were you that your acne medication products were working fast enough in clearing up the acne on your face?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

9. In the past WEEK, how bothered did you feel about the need to always have medication or cover-up available for the acne on your face?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

10. In the past WEEK, how much was your self-confidence (sure of yourself) negatively affected because of your facial acne?

    ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

11. In the past WEEK, how concerned or worried were you about meeting new people because of your facial acne?

    ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

12. In the past WEEK, how concerned or worried were you about going out in public because of your facial acne?

    ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

13. In the past WEEK, how much was socializing with people a problem for you because of your facial acne?

☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

14. In the past WEEK, how much was interacting with the opposite sex (or same sex if gay or lesbian) a problem for you because of your facial acne?

☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

15. In the past WEEK, how many bumps did you have on your face?

☐Extensive ☐A whole lot ☐A lot ☐A moderate amount ☐Some ☐Very few ☐None

16. In the past WEEK, how many bumps full of pus did you have on your face?

☐Extensive ☐A whole lot ☐A lot ☐A moderate amount ☐Some ☐Very few ☐None

17. In the past WEEK, how much scabbing from your facial acne did you have?

☐Extensive ☐A whole lot ☐A lot ☐A moderate amount ☐Some ☐Very few ☐None

18. In the past WEEK, how concerned or worried were you about scarring from your facial acne?

☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

19. In the past WEEK, how oily was your facial skin?

☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

Fecha: _____

Cuestionario sobre la calidad de vida, específico al acné

No. de Identificación: ☐

(Favor de marcar una casilla para cada pregunta)

1. Durante la SEMANA pasada, ¿qué tan **poco atractivo(a)** te sentiste debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

2. Durante la SEMANA pasada, ¿qué tan **avergonzado(a)** te sentiste debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

3. Durante la SEMANA pasada, ¿qué tan **acomplejado(a),** [incómodo(a) contigo mismo(a)], te sentiste debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

4. Durante la SEMANA pasada, ¿qué tan **disgustado(a)** te sentiste por tener acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

5. Durante la SEMANA pasada, ¿qué tan **molesto(a)** te sentiste por tomar tanto tiempo diariamente limpiándote y tratándote la cara, debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

6. Durante la SEMANA pasada, ¿qué tan **insatisfecho(a)** te sentiste con tu aspecto personal, debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

7. Durante la SEMANA pasada, ¿qué tan **intranquilo(a) o preocupado(a)** estuviste de no verte lo mejor posible, debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

(Favor de marcar una casilla para cada pregunta)

8. Durante la SEMANA pasada, ¿qué tan **intranquilo(a) o preocupado(a)** estuviste de que los medicamentos y productos para el acné estuviesen funcionando lo suficientemente rápido para eliminar el acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

9. Durante la SEMANA pasada, ¿qué tan **molesto(a)** te sentiste por la necesidad de tener siempre disponibles medicamentos o cremas para cubrir el acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

10. Durante la SEMANA pasada, ¿qué tan **negativo** fue el efecto del acné en tu confianza en ti mismo(a)?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

11. Durante la SEMANA pasada, ¿qué tan **intranquilo(a) o preocupado(a)** te sentiste al conocer a nuevas personas, debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

12. Durante la SEMANA pasada, ¿qué tan **intranquilo(a) o preocupado(a)** te sentiste al salir y estar entre la gente, debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

13. Durante la SEMANA pasada, **¿qué tan problemático fue para ti socializar con las personas,** debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

14. Durante la SEMANA pasada, **¿qué tan problemático fue para ti relacionarte con personas del sexo opuesto** (o del mismo sexo, para homosexuales), debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

(Favor de marcar una casilla para cada pregunta)

15. Durante la SEMANA pasada, ¿cuántos **granos** tenías en la cara?

abundantes	una gran cantidad	muchos	una cantidad moderada	algunos	muy pocos	ninguno
☐	☐	☐	☐	☐	☐	☐

16. Durante la SEMANA pasada, ¿cuántos **granos infectados** tenías en la cara?

abundantes	una gran cantidad	muchos	una cantidad moderada	algunos	muy pocos	ninguno
☐	☐	☐	☐	☐	☐	☐

17. Durante la SEMANA pasada, ¿cuántas **costras o postillas (espinillas secas)** tenías, debido al acné de la cara?

abundantes	una gran cantidad	muchas	una cantidad moderada	algunas	muy pocas	ninguna
☐	☐	☐	☐	☐	☐	☐

18. Durante la SEMANA pasada, ¿qué tan **intranquilo(a) o preocupado(a)** estuviste por las marcas y o cicatrices, que quedaron del acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

19. Durante la SEMANA pasada, ¿qué tan **grasoso** estaba el cutis?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

Protocol V01-121A-302 (IDP-121)

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris

Sponsor:

Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals, NA
1330 Redwood Way
Petaluma, CA 94954

SUMMARY OF CHANGES
Protocol V01-121A-302
Amendment 1, 20 August 2015

Additions marked in **bold**, deletions marked in ~~strikethrough~~.

Section	Page	Description of Change or Clarification	Rationale
As applicable	As applicable	Update to revision chronology, footers	Administrative changes
2	10	Deleted "~~and serum pregnancy testing~~"	Removal of requirement for serum pregnancy testing*
7.1	18, 20	Deleted "~~Serum pregnancy tests will also be conducted at Screening and Week 12~~"; Deleted "~~Serum Pregnancy Test (FOCBP)~~" line item in Schedule of Assessments.	Removal of requirement for serum pregnancy testing*
11.1.1	31, 32	Deleted "~~and Serum Pregnancy Test~~". Deleted "~~At the Screening and Week 12 visits, serum pregnancy testing is mandatory for all females of childbearing potential. In addition, a~~"	Removal of requirement for serum pregnancy testing*
11.1.4	34	Deleted "~~collect a blood sample for a serum pregnancy test and~~".	Removal of requirement for serum pregnancy testing*
11.3.4	38	Deleted "~~serum pregnancy testing at Screening and Week 12. In addition,~~".	Removal of requirement for serum pregnancy testing*

*Detailed rationale for removal of serum pregnancy testing:

- Initial protocol (submitted to FDA as part of pIND mtg) did not include serum pregnancy testing (only UPT)
- Sponsor subsequently added in serum testing (Baseline and Week 12), to be conservative in the approach with regard to retinoids – this version of protocol (V01-121A-301) was submitted in the IND package on 24-July-15
- Subsequent review of whole protocol, and Investigator feedback considered the following points to allow for removal of the serum pregnancy testing requirement:
  - UPTs allow for sensitivity of ~99.6%
  - UPTs will be performed at all study visits (Screening, Baseline, Week 4, Week 8 and Week 12). The chance for multiple false negatives is low. If at any point during the study a subject becomes pregnant, the subject must discontinue use of the study drug.
  - There are no safety labs being conducted in this study, so this blood sample would be the only draw for the study. This may preclude female subjects from entering the study (particularlyin the 10-14 age range).
- The study drug is a topical retinoid (tretinoin, 0.05%), considered Category C.

Protocol V01-121A-302 (IDP-121)

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris

Sponsor:

Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals, NA
1330 Redwood Way
Petaluma, CA 94954

SUMMARY OF CHANGES
Protocol V01-121A-302
Amendment 2, 28 September 2015

Additions marked in **bold**, deletions marked in ~~strikethrough~~.

Section	Page	Description of Change or Clarification	Rationale
As applicable	As applicable	Update to revision chronology, footers	Administrative changes
1 11.4.6	3 42	Added Office phone number for medical monitor, "**Office:** [redacted]	Additional information for medical monitor contact
2	5, 6, 7, 8, 9	Added "**Blood samples will be collected from subjects for safety monitoring at Baseline and Week 12.**" Replaced reference to ~~**Appendix 2**~~ with **Appendix 17.2.** Revised secondary efficacy variables to include: (1) Percent change in inflammatory lesion count from Baseline to Week 12 (2) Percent change in non-inflammatory lesion count from Baseline to Week 12 And added Supportive Efficacy to include: • Proportion 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 inflammatory lesion count from Baseline to Week 8 • Percent change in non-inflammatory lesion count from Baseline to Week 8 • Proportion of subjects who have at least a 2 grade reduction at Week 8 from Baseline in the Evaluator's Global Severity Score • Percent change in inflammatory lesion count from Baseline to Week 4 • Percent change in non-inflammatory lesion count from Baseline to Week 4 • Proportion of subjects who have at least a 2 grade reduction at Week 4 from Baseline in the Evaluator's Global Severity Score	Requested recommendation from agency in Study May Proceed letter (dated 10-Sep-15); Typo fix; Revision per requested recommendation from agency in Study May Proceed letter (dated 10-Sep-15)

		Added **hypo/hyper-pigmentation** to cutaneous safety assessments; Added **Changes from baseline in all safety laboratory values will be summarized using descriptive statistics by treatment group**. Added: **Additional supportive efficacy endpoints (including mean percent change in inflammatory and non-inflammatory lesions counts from baseline at Weeks 4 and 8, as well as proportion of subjects with at least a two grade improvement in the Evaluator's Global Severity Score from baseline at Weeks 4, 8 and 12) will be conducted, as noted above.** Added **Changes from baseline in safety laboratory values and vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits. Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at Baseline and Week 12. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at Week 12 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.**	Revision per requested recommendation from agency in Study May Proceed letter (dated 10-Sep-15)
7.1	19, 21	Added **and safety labs** Added line item for "**Safety labs (hematology, CBC/diff, urinalysis)"**	Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15
8.2	23	Added "at the prescribed amounts" to exclusion criteria #12	Typo updated for consistency with synopsis section
9.4	28	Added "**non-medicated**" and "**and, sunscreens**"	To clarify that skin care product use must be nonmedicated
11.1.1	32	Added "**cleansers**"	Clarification of allowed skin care products
11.1.2 11.1.4	33 35	Added "**blood pressure, heart rate, respiration rate, and oral temperature**" Added line item for: **Collect blood samples for routine laboratory analysis (CBC/Diff, serum chemistry and urinalysis)**	Clarification of vital signs; Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15
11.3.1	37, 38	Added **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.** Added **Hypopigmentation and Hyperpigmentation scale.**	Clarification of cutaneous safety assessments and recommendation from agency in Study May Proceed letter dated 10-Sep-15
11.3.4	39	Added Section for **Laboratory Tests**	Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15
11.4.2	40	Added "**Any AEs deemed related to treatment reported or observed at the final study/treatment visit will be followed until stabilization or resolution**	Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15

		(or up to 30 days after final study visit).”	
12.1.2	45	Deleted bullet point “~~Proportion of subjects who have at least a 2 grade reduction at Week 12 from baseline in the Evaluator’s Global Severity Score~~” from Secondary Efficacy and added it to **Section 12.1.3 Supportive Efficacy** endpoints	Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15
12.1.5	47	Edited Secondary Endpoint table to remove ~~step numbers 3-9~~, and added to a new **Secondary Supportive Endpoint** table; also added: **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:**	Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15
12.1.8	50, 51, 52	Added **Syntax** code; Added: **A total of 4 random seeds will be needed to impute inflammatory lesion counts from 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-121 Lotion: Seed= 1028933764** • **Inflammatory Lesion Counts; IDP-121 Vehicle: Seed= 356782065** • **Non-Inflammatory Lesion Counts; IDP-121 Lotion: Seed= 1307444541** • **Non-Inflammatory Lesion Counts; IDP-121 Vehicle: Seed= 436373460** Added**: 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-121 Lotion: Seed= 1210644108** • **EGSS; IDP-121 Vehicle: Seed= 763715437**	Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15
12.1.9	52, 53	Added: **Although the full details will be presented in the Statistical Analysis Plan (SAP), the multiple**”	Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15
12.2	53	Added “**and hypo/hyper-pigmentation**”	Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15
12.2.2	54	Added **Section for Safety Laboratory Tests**	Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15
App 17.2	66	Deleted “~~only~~”; Added “**as examples of approved products**”, “**the below set of examples or other**”, “**non-medicated**”	Revision per recommendation from agency in Study May Proceed letter dated 10-Sep-15

Protocol V01-121A-302 (IDP-121)

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris

Sponsor:

Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals, NA
1330 Redwood Way
Petaluma, CA 94954

SUMMARY OF CHANGES
Protocol V01-121A-302
Amendment 3, 7 October 2016

Additions marked in **bold**, deletions marked in ~~strikethrough~~.

Section	Page	Description of Change or Clarification	Rationale
As applicable	As applicable	Update to revision chronology, footers	Administrative changes
1,11.4.6	3, 43	Update to mobile phone number for medical monitor, from [redacted] to "[redacted]"	Updated contact information for medical monitor
1;11.4.6	3, 42	Replaced CRO Project Manager name and contact from [redacted] ~~Sr. Project Manager~~ [redacted] To [redacted] **Project Manager** [redacted] **Fax number: N/A** [redacted]	Change in CRO Project Manager
2, 12.8.4	5, 57	Added "**and Latin America**"	Added Latin America sites to the study
2,7.1, 10.1.3	5, 19, 31	Added Globally 12 weeks "**(up to week 12 visit).**"	Added for more clarification
2, 11.3.4, 11.3.5	5, 39	Added Globally week 12 "**visits**"	Added for more clarification
2	7	Replaced ~~Antiobioties~~ to **Antibiotics**	Correction of spelling
2, 9.5, 10.1.1, 10.2, 11.1.2,	21, 28, 30, 32, 34, 35	Added Globally **"(with the cap on) to the nearest 0.1 gram"**	Added for more clarification and consistency

11.1.3, 11.1.4			
8.3	25	Added Pregnancy – Subject will discontinue study drug immediately, but will be followed to term. Complete pregnancy **and SAE** form**s.**	Added for more clarification for pregnancy reporting
9.4	27-28	Updated Any concomitant **medication or** therapy stopped for washout as indicated below is to be recorded. 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. Information on concomitant **medications or** therapies will be recorded in the Prior and Concomitant Medication or Therapy source document and eCRF. Any therapy used by the subject will be considered concomitant therapy **(e.g., Facial procedures, surgical procedures, investigations and operations) and any medication both over the counter (OTC) or prescription used by the subject will be considered concomitant medication** (eg, aspirin, Tylenol, birth control pills, vitamins, moisturizers, sunscreens). 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 Medication or Therapy source document and eCRF. All cleansers and moisturizers and other topical products used on the treatment area that are not prescription products will be captured on the ~~Other Skin Care Products~~ **Concomitant Medication** source document and eCRF	Updated section to add clarification and to be consistent with the eCRF guidelines and how this information should be captured
11.4.8	44	Added All confirmed pregnancies must be reported via confirmed facsimile/email transmission and must be submitted on a **SAE and pregnancy report** form**s** within 24 hours of the investigator's awareness of the pregnancy using the same reporting as procedure for an SAE under Section 11.4.6.	Added for more clarification for pregnancy reporting
12.1.10	53	Updated Subset analyses will be conducted for the ITT populations for the subgroups baseline global severity, gender, age, ethnicity~~, and~~ race**, and geographic location.** Age will be dichotomized to less than the median age of subjects and greater than or equal to the median age of subjects. An	Addition of outside US Geographic region due to addition of Latin America sites.

		additional analysis will be include with categories of less than 18, 18 to less than the median age and greater than or equal to the median age. **Geographic region will be dichotomized to US and outside US (OUS).**	
12.5	55	Replaced A ~~tabulation~~ of protocol deviations will be included in the final study report. With A **listing** of protocol deviations will be included in the final study report	Correction on format of protocol deviations in the study report

CLINICAL STUDY PROTOCOL

IDP-121

Protocol V01-121A-302

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris

Development Phase:	3
Study Design:	Multi-center, randomized, double-blind, vehicle-controlled efficacy and safety study
Date:	07 October 2016 (Amendment 3)
Sponsor:	Dow Pharmaceutical Sciences, a Division of Valeant Pharmaceuticals North America, LLC 1330 Redwood Way Petaluma, CA 94954 [redacted]

CONFIDENTIAL

Nothing herein is to be disclosed without prior approval of the sponsor.

VALEANT
Research & Development

Protocol Review and Approvals

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety ofIDP-121 and **IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris**

Reviewed and approved:

[redacted]

11 - \ - 2ci in.
Date

[redacted]
Va1eant Pharmaceuticals North America, LLC

23 0 c.i -k/e.
Date

[redacted]
Valeant Pharmaceuticals North America, LLC

[redacted]

11/1 /wtb
Date

[redacted]
Valeant Pharmaceuticals North America, LLC

Personnel Responsible for Conducting the Study

A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris

Contract Research Organization

[redacted]
Medical Monitor

TKL Research, Inc.
365 W. Passaic Street, Suite 550
Rochelle Park, NJ 07662

[redacted]

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Project Manager

TKL Research, Inc.
365 W. Passaic Street, Suite 550
Rochelle Park, NJ 07662

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Fax number: N/A
[redacted]

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-121 Lotion

Name of Active Ingredients: Tretinoin 0.05% lotion

Title of Study: A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 Lotion and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris

Number of clinical centers: Multicenter, approximately 32-50 investigational centers in North America and Latin America

Objective:

The primary objective of this study is to compare the efficacy, safety and tolerability of IDP-121 Lotion and vehicle in the treatment of subjects with acne vulgaris.

Methodology:

This is a multicenter, randomized, double-blind, parallel group, vehicle-controlled, 12-week study to evaluate relative changes in inflammatory and non-inflammatory lesion counts, as well as treatment success using an Evaluator's Global Severity Scale (EGSS) in subjects with moderate to severe acne. Subjects must be at least 9 years of age and older with moderate to severe acne vulgaris (a score of 3 or4 [moderate to severe] on the EGSS scale), presenting with 20-40 inflammatory facial lesions (papules, pustules, and nodules), 20-100 non-inflammatory facial lesions (open and closed comedones), and $\leq$ 2 facial nodules.

Approximately eight hundred (800) subjects will be randomized to the following treatment groups:

- 400 Subjects to IDP-121 Lotion, once-daily application
- 400 Subjects to IDP-121 Vehicle Lotion, once-daily application

All subjects will receive once daily, topically-applied treatment to the face for 12 weeks (up to week 12 visit). Subject visits include Screening, Baseline, Week 4, Week 8, and Week 12, at which safety and efficacy assessments will be conducted. Blood samples will be collected from subjects for safety monitoring at Baseline and Week 12 visits.

Number of subjects planned:

Approximately 800 subjects will be randomized to the following treatment groups:

- 400 Subjects to IDP-121 Lotion, once-daily application
- 400 Subjects to IDP-121 Vehicle Lotion, 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 screening and baseline visit;
4. Subjects with facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 20 but no more than 40;
5. Subjects with facial acne non-inflammatory lesion (open and closed comedones) count no less than 20 but no more than 100;
6. Subjects with two or fewer facial nodules;

7. Women of childbearing potential and females that 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 or abstinence.) Females on birth control pills must have taken the same type pill for at least three months prior to entering the study and must not change type during the study. Those who have used birth control pills in the past must have discontinued usage at least 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 women 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). If the subject wears makeup they must agree to use non-comedogenic makeup.

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;
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 estrogens (eg, Depogen, Depo-Testadiol, Gynogen, Valergen, etc) for less than 12 weeks immediately preceding study entry; Subjects treated with estrogens 12 or more consecutive weeks immediately prior to study entry need not be excluded unless the Subject expects to change dose, drug or discontinue estrogen use during the study;
10. If female, subject has a history of hirsutism, polycystic ovarian disease or clinically significant menstrual irregularities;
11. Treatment of any type of cancer within the last 6 months;
12. Subject uses medications and/or vitamins during the study which are reported to exacerbate acne (azothiaprim, haloperidol, Vitamin D, Vitamin B12, halogens such as iodides or bromides, lithium, systemic or mid-to super-high potency corticosteroids, phenytoin and phenobarbital); Daily vitamins at the prescribed amounts 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;
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 that have not undergone the specified washout period(s) for the following topical preparations used on the face or subjects who require the concurrent use of any of the following topical agents in the treatment area:

Topical astringents and abrasives on face	1 week
Antibiotics on the facial area	2 weeks
Non-allowed moisturizers or sunscreens on face	2 weeks
Other topical anti-acne drugs on face	2 weeks
Soaps containing antimicrobials on the face	2 weeks
Anti-inflammatory agents and corticosteroids on the facial area	4 weeks
Retinoids, including retinol on the face	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 and must be noted in source documents and eCRF.

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

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

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-121 (tretinoin 0.05%) Lotion, applied topically to the face, once daily for 12 weeks.

Comparator Product: IDP-121 Vehicle Lotion, 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-121 Lotion versus IDP-121 Vehicle Lotion

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) Percent 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:

(1) Percent change in inflammatory lesion count from Baseline to Week 12
(2) Percent change in non-inflammatory lesion count from Baseline to Week 12

Supportive Efficacy:

- Proportion of subjects who have at least a 2 grade reduction at Week 12 from Baseline inthe Evaluator's Global Severity Score
- Percent change in inflammatory lesion count from Baseline to Week 8
- Percent change in non-inflammatory lesion count from Baseline to Week 8
- Proportion of subjects who have at least a 2 grade reduction at Week 8 from Baseline inthe Evaluator's Global Severity Score
- Percent change in inflammatory lesion count from Baseline to Week 4
- Percent change in non-inflammatory lesion count from Baseline to Week 4
- Proportion of subjects who have at least a 2 grade reduction at Week 4 from Baseline inthe 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 – a small, solid elevation less than 5 mm in diameter. Most of the lesion is above the surface of the skin.

Pustule – a small, circumscribed elevation less than 5 mm in diameter that contains yellow-white exudate.

Nodule – a subcutaneous lesion greater than or equal to 5 mm in diameter

Non-inflammatory lesions are defined as follows:

Open comedones (black head) - a lesion in which the follicle opening is widely dilated with the contents protruding out onto the surface of the skin.

Closed comedones (white head)– a lesion in which the follicle opening is closed, but the sebaceous gland is enlarged by the pressure of the sebum build up, which in turn causes the skin around the follicle to thin and become elevated 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

Cutaneous safety and tolerability will be evaluated by tabulations of adverse events and Cutaneous Safety and Tolerability Evaluation scores (scaling, erythema, hypo/hyper-pigmentation, itching, burning, and stinging) to be assessed at each study visit. Itching, burning and stinging (Cutaneous tolerability) will be reviewed with the subject at each study visit as an average over the period since the previous visit. Scaling, erythema and hypo/hyper-pigmentation (Cutaneous Safety) will be assessed by the evaluator at each visit. Changes from baseline in all safety laboratory values will be summarized using descriptive statistics by treatment group.

Cutaneous tolerability signs and symptoms that result in the subject requiring 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 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. Finally, the absolute change in lesion count will 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.

The co-primary analysis of the dichotomized EGSS will be based on the logistic regression test stratified by analysis center.

Populations Analyzed and Treatment Groups:

Inflammatory and non-inflammatory lesion counts will be recorded for each Subject at Baseline and at Weeks 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 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 4, 8, and 12 is at least 2 grades less than baseline and Clear or Almost Clear.

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

The safety population will be comprised of all randomized subjects who are presumed to have used the study medication at least once and who provide at least one post-baseline evaluation. A per-protocol (PP) analysis will also be conducted. Subjects will be eligible for the PP analysis if they complete the 12-week evaluation without noteworthy study protocol violations (i.e., any Subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy). The PP population will include subjects in the ITT population who do not meet any of the following criteria:

- Failed any of the inclusion/exclusion criteria;
- Have taken any interfering concomitant medications;
- Did not attend the Week 12 visit, with the exception of a discontinuation from the study due to an adverse event related to study treatment or documented lack of treatment effect;
- Missed both the week 4 and week 8 visits;
- 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

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 eight hundred (800) subjects will be randomized to the following treatment groups:

- 400 Subjects to IDP-121 Lotion, once-daily application
- 400 Subjects to IDP-121 Vehicle Lotion, once-daily application

Efficacy:

Primary:

Co-primary efficacy analyses of the absolute change in inflammatory and in non-inflammatory lesions will be conducted on the ITT population. The pre-specified time point will be Week 12. Descriptive statistics will be presented by treatment group for inflammatory and for non-inflammatory lesions as well as the absolute change in inflammatory and in non-inflammatory lesions. All of the testing relating to the analysis of inflammatory and non-inflammatory lesions will use the methods introduced in Section 12.

The co-primary analysis of the dichotomized EGSS (success being at least a 2 grade improvement and achieving Clear or Almost Clear) for the ITT population will be based on the logistic regression test stratified by analysis center.

Secondary:

Mean percent change in inflammatory and non-inflammatory lesion counts from baseline to Week 12.

Supportive:

Additional supportive efficacy endpoints (including mean percent change in inflammatory and non-inflammatory lesions counts from baseline at Weeks 4 and 8, as well as proportion of subjects with at least a two grade improvement in the Evaluator's Global Severity Score from baseline at Weeks 4, 8 and 12) will be conducted, as noted above.

Safety Evaluation:

All subjects who receive medication and provide at least one post-baseline evaluation will constitute the safety population.

Safety will be evaluated by tabulations of adverse events (AEs), Cutaneous 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 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 and an abbreviated physical exam, and safety labs will be conducted on all subjects at specified visits. For females of child-bearing potential (FOCBP), urine pregnancy testing will occur at specified visits. Changes from baseline in safety laboratory values and vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits. Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at Baseline and Week 12. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at Week 12 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 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 medication, the action taken regarding study medication 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 medication. 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 proportion 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 medication.

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

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

Subject Self-Assessments

An exploratory patient self assessment questionnaire and satisfaction survey will also be administered during the study.

Subjects will be asked to complete three questionnaires during the study: the Subject Self Assessment scale, the Patient Satisfaction Survey and the Acne-Specific Quality of Life Questionnaire. The Investigator assessments (EGSS, lesion counts) will be conducted independently of these subject self assessments. The EGSS should always be completed prior to the lesion counts. Inferential statistical analysis will not be performed on these questionnaires; 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
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
cGCP	Current Good Clinical Pratice
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
IATL	Investigator's Assessment of Total Lesions
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Affairs
mL	Milliliter
OTC	Over-the-counter
PP	Per protocol
PSS	Patient Satisfaction Survey
QoL	Quality of Life
SAE	Serious adverse event
SSA	Subject Self Assessment
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 (all-trans-retinoic-acid) is a member of the retinoid family of compounds and is a metabolite of Vitamin A that occurs naturally in animal and human tissues. While oral retinoids (eg, isotretinoin) are reserved for treatment of severe nodular acne or severe acne resistant to oral antibiotics, topical retinoids (eg, tretinoin or isotretinoin) applied daily are used to inhibit the formation of comedones and usually clear even severe comedonal acne within a few months [6]. Topical formations of tretinoin have been used to treat acne in the United States (US) and the European Union for more than 25 years.

Tretinoin binds with high affinity to specific retinoic acid receptors located in both the cytosol and nucleus, but cutaneous levels of tretinoin in excess of physiologic concentrations occur following application of a tretinoin-containing topical drug product. Tretinoin activates 3 members of the retinoid acid (RAR) nuclear receptors (RARα, RARβ, and RARγ) which act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation; however, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms, or both. Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

IDP-121 is a lotion containing 0.05% tretinoin for the topical treatment of acne. This proposed product is the first lotion formulation developed for tretinoin and will be evaluated for effectiveness in treating acne vulgaris.

6 Study Objectives and Purpose

The objective of the study is to evaluate the efficacy, safety and tolerability of a once-daily topical application of IDP-121 Lotion compared to its vehicle (IDP-121 Vehicle Lotion) in subjects with moderate to severe acne vulgaris (a score of 3 or 4 [moderate to severe] on the EGSS scale).

7 Investigational plan

7.1 Overall Study Design and Plan: Description

This is a multicenter, randomized, double-blind, parallel-group study designed to assess the safety, efficacy and tolerability of IDP-121 Lotion in comparison with its vehicle. 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 800 subjects will be enrolled into this study and randomized into one (1) of two (2) treatment groups: 400 subjects in the IDP-121 Lotion, once daily application group,

and 400 subjects in the IDP-121 Lotion Vehicle, once daily application group. Subjects will be enrolled at a minimum of 32 and maximum of 50 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 4, 8, and 12).

An interactive web based response system (IWRS) will be employed to facilitate randomization of study patients. Treatment assignments and study drug kit numbers will be generated centrally by the IWR system. 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 for 12 weeks (up to week 12 visit). The initial application will be made 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. Subjects will apply their daily treatments at home as explained by the study coordinator or designee at each investigational center. During post-baseline study visits (Weeks 4, 8 and 12) the subjects will be asked to return their used tubes of study drug and will be dispensed new tubes of study drug (only Weeks 4 and 8; 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 three questionnaires during the study: the Subject Self Assessment scale (SSA, Appendix 17.3), the Patient Satisfaction Survey (PSS, Appendix 17.4) and the Acne-Specific Quality of Life Questionnaire (Acne-QoL, Appendix 17.5). The Investigator assessments (EGSS, lesion counts) will be conducted independently of these subject self assessments. The EGSS should be completed prior to the lesion counts. Subjects will assess the severity of their acne at the baseline visit and at Weeks 2 (at home), 4, 8, and 12 by completing the SSA. The Week 2 SSA form will be dispensed to the subject at the baseline visit with instructions to complete it two weeks later and return it the Week 4 visit; sites should call the Subject at Week 2 to remind them to complete the SSA. Subjects will complete the PSS related to prior therapy at baseline, and at Week 12 will complete the PSS related to current study medication. The Acne-QOL will be completed at baseline and Week 12. Inferential statistical analysis will not be performed on these questionnaires; the subjective responses will be compared between treatment groups for trends.

Information on reported and observed adverse events (AEs) will be obtained at each visit. An abbreviated physical examination and safety labs will be performed at Baseline and Week 12 (end of treatment, final visit) for all subjects.

For all female subjects of childbearing potential, urine pregnancy testing will be performed at Screening and confirmed at Baseline with a urine pregnancy test prior to randomization, and at Weeks 4, 8 and 12.

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.

Table 1. Study Design and Schedule of Assessments

PROCEDURES	VISIT 1[1] Screening Visit	VISIT 2[2] Baseline Day 0	VISIT 3[2] Week 4 (Day 28 ±3 days)	VISIT 4[2] Week 8 (Day 56 ± 3 days)	VISIT 5[2,3] Week 12 (Day 84 -3/+5 days)
Informed consent/Assent	X				
Obtain Subject Number from IWRS	X				
Demographics	X				
Medical history	X	X			
Inclusion/Exclusion criteria	X	X			
Previous therapies	X				
PSS & Acne-QoL		X			X
SSA[4]		X	X	X	X
Urine Pregnancy Test (UPT) (FOCBP)	X	X	X	X	X
Abbreviated physical examination and vital signs		X			X
Safety labs (hematology, CBC/diff, urinalysis)		X			X
Oily/shiny skin assessment		X			X
Lesion Counts	X	X	X	X	X
EGSS	X	X	X	X	X
Photographs (select sites only)		X			X
Cutaneous Safety Evaluation		X	X	X	X
Tolerability Evaluation		X	X	X	X
Randomization in IWRS (obtain kit #)		X	X	X	
Administer Subject Instructions (Appendix 17.1)		X			
Dispense Study Drug[5]		X	X	X	
Weigh Study Drug to the nearest 0.1gram		X	X	X	X
Study Drug applied at investigational center		X			
Study Drug Collected			X	X	X
Subject Diary Calendar dispensed		X	X	X	
Subject Compliance Reviewed / Diary			X	X	X
Adverse Events	X	X	X	X	X
Concomitant Therapy and Prohibited Therapies Review	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] All visit dates are in reference to baseline, e.g., Visit 4 occurs 8 weeks +/- 3 days after baseline visit.
[3] All Week 12 procedures should be completed for all subjects who terminate early.
[4] The Week 2 SSA will be sent home with the subject during the baseline visit (Visit 2) with instructions to complete it at two weeks and return it at the Week 4 visit. The site should call the subject at Week 2 to remind them to take the Week 2 SSA.
[5] Dispense one tube of test material at the Baseline, Week 4 and Week 8 visits.

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 assessment at the screening and baseline visit;
4. Subjects with facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 20 but no more than 40;
5. Subjects with facial acne non-inflammatory lesion (open and closed comedones) count no less than 20 but no more than 100;
6. Subjects with two or fewer facial nodules;
7. Females of childbearing potential[1] and females that 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 or abstinence.) Females on birth control pills must have taken the same type pill for at least three months prior to entering the study and must not change type during the study. Those who have used birth control pills in the past must have discontinued usage at least 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 medication. Kits will be provided by the CRO.

moisturizer/sunscreen combination products (see Appendix 17.2). If the subject wears makeup they must agree to use non-comedogenic makeup.

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;
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 estrogens (eg, Depogen, Depo-Testadiol, Gynogen, Valergen, etc) for less than 12 weeks immediately preceding study entry; Subjects treated with estrogens 12 or more consecutive weeks immediately prior to study entry need not be excluded unless the Subject expects to change dose, drug or discontinue estrogen use during the study;
10. If female, subject has a history of hirsutism, polycystic ovarian disease or clinically significant menstrual irregularities;
11. Treatment of any type of cancer within the last 6 months;
12. Subject uses medications and/or vitamins during the study which are reported to exacerbate acne (azothiaprim, haloperidol, Vitamin D, Vitamin B12, halogens such as iodides or bromides, lithium, systemic or mid-to super-high potency corticosteroids, phenytoin and phenobarbital); Daily vitamins at the prescribed amounts 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;
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 that have not undergone the specified washout period(s) for the following topical preparations used on the face or subjects who require the concurrent use of any of the following topical agents in the treatment area :

Topical astringents and abrasives on face	1 week
Antibiotics on the facial area	2 weeks
Non-allowed moisturizers or sunscreens on face	2 weeks
Other topical anti-acne drugs on face	2 weeks
Soaps containing antimicrobials on the face	2 weeks
Anti-inflammatory agents and corticosteroids on the facial area	4 weeks
Retinoids, including retinol on the face	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 and must be noted in source documents and eCRF.

16. Subjects that 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 (eg, severe adverse reactions), or at the subject's request.
- When the requirements of the protocol are not followed.
- When a concomitant therapy likely to interfere with the results of the study is reported, or required by the subject (the investigators will report all such information

on the source documents/case report forms (CRFs) and decide, in accordance with the sponsor, whether the subject is to be withdrawn).

- When a subject is lost to follow-up. The investigators will try twice to reach the subject by telephone and will send a follow-up letter by certified mail before considering that the subject is lost to follow-up. These actions will be reported on the End of Study CRF 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 the final CRF, and, if need be, on the AE form. In any case, no subject who has been included and has a study 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 2 phone calls and a certified letter.

Pregnancy – Subject will discontinue study drug immediately, but will be followed to term. Complete pregnancy and SAE forms.

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 CRF.

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 study drug groups in a ratio of 1:1 (IDP-121 [tretinoin 0.05%] Lotion : IDP-121 Vehicle Lotion). 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 (eg, 101001, 101002). The study drug kit will be assigned to subjects based on a randomization code and kit will be dispensed to the subjects at Baseline by the IRW system, and at 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 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 tubes as scheduled.

9.3 Un-blinding

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. The investigator will record the code break in the subject's source documents.

9.4 Prior and Prohibited Concomitant Medication or Therapy

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

Topical astringents and abrasives on the face	1 week
Antibiotics on the facial area	2 weeks
Non-allowed moisturizers or sunscreens on the face	2 weeks
Other topical anti-acne drugs on the face	2 weeks
Soaps containing antimicrobials on the face	2 weeks
Anti-inflammatory agents and corticosteroids on the facial area	4 weeks
Retinoids, including retinol on the face	4 weeks

If the subject requires topical treatment for acne on areas other than the face (eg, chest or back), the investigator may prescribe a product that does not contain tretinoin and noted in 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 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 both over the counter (OTC) or prescription used by the subject will be considered concomitant medication (eg, aspirin, Tylenol, birth control pills, vitamins, moisturizers, sunscreens). 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 Medication or Therapy source document and eCRF.

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

Subjects should avoid excessive UV exposure by such activities as sun bathing or tanning booths.

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 tubes dispensed at each treatment visit to the next subsequent study visit. Each tube will be weighed (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. The subject will also be sent home with a Subject Self Assessment (SSA) survey at the Baseline visit, with instructions to complete it at home at two (2) weeks after their baseline visit, and return it at the Week 4 study visit.

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 patients or a small group of patients 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 patient, when the patient or investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria) and the patient was enrolled without prior sponsor approval, or when there is nonadherence to FDA regulations and/or ICH GCP guideline.

The investigator or designee must document and explain in the patients' 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 patients 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-121 Lotion and IDP-121 Vehicle Lotion

Chemical structure and formula for the active ingredients in IDP-121 Lotion and vehicle are listed in the tables below:

Table 2. Drug Substances Identification

Active Ingredient	Tretinoin 0.05%
Chemical Name	(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenoic acid
Chemical Class	Retinoid
Molecular Formula	$C_{20}H_{28}O_2$
CAS Registry Number	302-79-4

Table 3. Test Product Identification

	Investigational Product	Vehicle
Name of Active Ingredient	Tretinoin, EP / USP	N/A
Drug Name/Formulation/ Concentration	IDP-121 Lotion [Tretinoin 0.05%]	IDP-121 Vehicle Lotion
Manufacturer	Valeant Pharmaceuticals International, Inc. 2150 St. Elzear Boulevard West Laval (Quebec), Canada H7L 4A8	
Packaging	45 g tube	45 g tube
Storage Requirements	Store at 20°C to 25°C (68°F to 77°F)	Store at 20°C to 25°C (68°F to 77°F)
Appearance	Opaque pale yellow lotion	Opaque pale yellow lotion
Dosing Schedule	Once daily x 12 weeks	Once daily x 12 weeks
Route of Administration	Topical Application	Topical Application

10.1.1 Packaging and Labeling

IDP-121 Lotion and its vehicle 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 IWRS specific kit number will be assigned to be used for that randomized subject by the IWR system. Each subject kit will contain one tube, which has 45 grams of study material. A new subject kit will be assigned to a subject at each visit: Baseline, Week 4 and Week 8. The subjects will be dispensed one kit at Baseline as assigned in the IWR system. The tube will be weighed (with the cap on) to the nearest 0.1 gram prior to dispensing. The subject will bring the tube to the next study visit (Week 4), where it will be collected and weighed (with the cap on) to the nearest 0.1 gram; one new tube will be dispensed again by the IWR system at Week 4, weighed (with the cap on) to the nearest 0.1 gram and provided to the subject. The same will occur at the Week 8 visit. If the subject loses a tube (lost or damaged tube), another kit will be dispensed via IWRS. Each tube dispensing will be documented on the drug accountability log.

Each subject kit (and tube) will have a single panel label. Labels will contain the following information:

- Protocol Number
- Kit Number
- Contents
- Space for entry of the subject initials
- Space for entry of date dispensed
- The sponsor name, Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals N.A., LLC
- The quantity of product (45 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

Test material will be applied topically to the face once a day for a period of 12 weeks. Test material will be applied as a thin coating (a dab the size of a large pea) that is gently rubbed in to the skin. The test material use should 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 the test material at approximately the same time every day for 12 weeks (up to week 12 visit) after cleansing. On study visit days subjects should be instructed to wait until after their study visit to apply study medication. No time interval between dosing and meals or any other activity is specified. Subjects will be instructed to gently wash their face with a Sponsor approved 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 tube to dispense a pea-sized amount of study drug to their fingertip. This dose should then be dotted on to 6 areas (chin, left cheek, right cheek, nose, left forehead, right forehead) on the face. After distributing the dose in this manner the subject should gently rub the lotion 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.

The subjects will be instructed to continue using the same Sponsor approved 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 store the test material at room temperature.

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. Tubes will be weighed (with the cap on) to the nearest 0.1 gram before dispensing to and upon return by the subjects, and weights to the nearest 0.1 gram will be recorded on the pharmacy log and appropriate CRF. All used and unused supplies will be returned to sponsor/designee for destruction at the conclusion of the study.

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

The following procedures will be conducted at this visit:

1. Obtain written informed consent prior to performing any study procedures. Subjects less than 18 years of age 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 your site) and the 3-digit chronological order screening number, assigned by the IWR system and starting with 101 (eg, 101 001, 101 002, 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 Assessment followed by inflammatory lesion count and non-inflammatory lesion count to determine eligibility.
7. Perform a Urine Pregnancy Test for all females that are pre-menses and females of childbearing potential. The urine pregnancy tests will be supplied by the CRO.
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. Verify that the subject meets the applicable inclusion/exclusion criteria as outlined in Sections 8.1 and 8.2.
11. Remind subject to not apply test medication on day of next study visit prior to the clinic visit.
12. If the subject requires a washout, schedule the Baseline visit to occur after the washout is complete. If no washout is required, the Screening and Baseline visits may occur on the same day.
13. Schedule subject to return for the Baseline/Day 0 visit. If the subject requires a washout, schedule the Baseline/Day 0 visit to occur after the washout is complete.

NOTE: A urine pregnancy test must be completed at Screening and at the Baseline visit prior to randomization, and at Weeks 4, 8 and 12. The decision may be made by the investigator to do additional pregnancy tests during the course of the study.

11.1.2 Visit 2: Baseline Visit (Day 0)

If a washout is not needed, this visit may occur on the same day as the Screening Visit (Visit 1). If a washout is needed, Visit 2 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 Subject Self Assessment (SSA), Patient Satisfaction Survey (PSS) and the Acne-Specific Quality of Life Questionnaire (Acne-QoL) will be completed by the subject and collected prior to any other study-related procedures. The Week 2 SSA will be sent home with the subject with instructions to complete it at two weeks and return it at the Week 4 visit.
2. Verify that the subject continues to meet the applicable inclusion/exclusion criteria as outlined in Sections 8.1 and 8.2.
3. Record changes in any concomitant medications since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant therapies as per Section 9.4.
4. Perform a Urine Pregnancy Test for all females that are pre-menses and females of childbearing potential. The urine pregnancy tests will be supplied by the CRO.
5. Perform an abbreviated physical exam, including measurements of height and weight, and vital signs (blood pressure, heart rate, respiration rate, and oral temperature). Any abnormal physical exam findings will be recorded.
6. Collect blood samples for routine laboratory analysis (CBC/Diff, serum chemistry and urinalysis).
7. The Evaluator will query the subject regarding how oily/shiny their facial skin has been in the past week.

8. 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.
9. The Evaluator will perform Cutaneous Safety and Tolerability Evaluations.
10. Assign the subject the presented kit number (this number will be generated from the Interactive Web Response system, (IWRS)).
11. The study coordinator or designee will weigh the tube (with the cap on) to the nearest 0.1 gram within the assigned kit 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.
12. 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.
13. Record any AEs or changes in AEs since the screening visit and/or reported spontaneously by the subject.
14. *Selected Sites only* - Obtain representative photographs of the face.
15. Schedule the next study visit at Week 4 (Day 28 ± 3 days). Remind the subject to not apply test medication on day of next study visit, prior to the clinic visit.

11.1.3 Visit 3 and 4: Week 4 (Day 28 ± 3 Days) and Week 8 (Day 56 ± 3 Days) Visits

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

1. The take-home Week 2 SSA will be collected during the Week 4 study visit.
2. The Week 4 or Week 8 SSA will be conducted and collected.
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 since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant therapies as per Section 9.4.
6. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.

7. Perform a Urine Pregnancy Test for all females that are pre-menses and females of childbearing potential. The urine pregnancy tests will be supplied by the CRO.
8. The study drug technician will retrieve and weigh the used test material tube and assign the subject another kit number (this number will be generated from the Interactive Web Response system, (IWRS) and dispense a new subject kit of test material. The tube will be weighed on a calibrated scale. Record the weight (with the cap on) to the nearest 0.1 gram.
9. 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.
10. Schedule the subsequent study visit, as applicable. Remind the subject to not apply test medication on the day of the next study visit, prior to the clinic visit.

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

The following procedures will be conducted at this visit:

1. The Week 12 SSA, PSS and 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 height and weight, and vital signs (blood pressure, heart rate, respiration rate, and oral temperature). Any abnormal physical exam findings will be recorded.
3. Collect blood samples for routine laboratory analysis (CBC/Diff, serum chemistry and urinalysis).
4. The Evaluator will query the subject regarding how oily/shiny their facial skin has been in the past week.
5. 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.
6. The Evaluator will perform Cutaneous Safety and Tolerability Evaluations.
7. Record changes in any concomitant medications since the previous visit under Prior and Concomitant Medications or Therapies. Check for prior and concomitant therapies as per Section 9.4.
8. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
9. The study diary calendar will be collected and reviewed for compliance. Any missed doses or deviations should be reported.
10. The study drug technician will retrieve all test material tubes from the subject and weigh the tubes on a calibrated scale and record the weight (with the cap on) to the nearest 0.1 gram.

11. For women of child bearing potential, perform a final Urine Pregnancy Test for all females that are pre-menses and females of childbearing potential. The urine pregnancy tests will be supplied by the CRO.
12. *Selected Sites only* - Obtain representative photographs of the face.
13. Exit the subject from the study and complete the end of study CRFs.

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, the same Evaluator must 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 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. 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 – a solid, elevated lesion less than 5 mm
Pustule – an elevated lesion containing pus less than 5 mm
Nodule – palpable subcutaneous lesion greater than 5 mm; has depth, not necessarily elevated
Non-inflammatory lesions are defined as follows:

Open comedones (blackhead) – plugged hair follicle with dilated/open orifice; black in color
Closed comedones (whitehead) – plugged hair follicle: small opening at skin surface

11.2.3 Other Assessments

Oily/Shiny Face Assessment

The subject will be asked at Baseline and Week 12 to assess how oily their skin has been in the past week by the scale below:

Oily/Shiny skin assessment
- 0 – None No oily or shiny skin on face
- 1 – Mild Mild oily or shiny skin on face
- 2 – Moderate Definite oily or shiny skin on face
- 3 – Severe Extremely oily or shiny skin on face

If subject answers 1, 2 or 3 to the above they will also be asked how often the oily skin made them feel bothered during the past week with scale below:
- 0 – Not bothered at all
- 1 – A little bothered
- 2 – Moderately bothered
- 3 – Very bothered
- 4 – Extremely bothered

Photography

At select sites, photographs of the face will be taken at Baseline and Week 12, at a minimum. 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 at the time of the visit.

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.

(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 will consist of measurements of height and weight, and vital signs (blood pressure, heart rate, respiration rate, and oral temperature) and will be performed at Baseline and Week 12 (end of treatment/study). Any abnormal physical exam findings will be recorded.

11.3.4 Laboratory Tests

Clinical laboratory analyses (CBC/Diff, serum chemistry, and urinalysis) will be conducted on blood samples collected from subjects at Baseline and Week 12 visits. 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.

11.3.5 Pregnancy Tests

All female subjects of childbearing potential will undergo urine pregnancy testing at Screening and prior to randomization at Baseline, and at Week 4, 8 and Week 12 visits. The urine pregnancy tests will be supplied by the CRO.

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 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 CRF:

- 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 will be considered an SAE, 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: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

- Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required
- Severe: Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible; may be incapacitating or life threatening

11.4.5 Assessment of Causality

The investigator should assess the relationship of the AE, if any, to the study drug as either "Related" or "Not Related". The following should be taken into account when assessing 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 within 24 hours of the investigator's awareness of the event. All SAEs must be reported via confirmed facsimile and 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:

[redacted] Medical Monitor

&

[redacted] Project Manager [TKL Research, Inc.]

Fax: N/A

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 CRF 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 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 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, 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.

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 or Package Insert) 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 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 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 within 24 hours of the investigator's awareness of the pregnancy. All confirmed pregnancies must be reported via confirmed facsimile/email transmission and must be submitted on a SAE and pregnancy report forms within 24 hours of the investigator's awareness of the pregnancy using the same reporting as procedure for an SAE under 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. Finally, the absolute change in lesion count will 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.

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 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 4, 8, and 12.

The EGSS will be recorded for each Subject. The EGSS will be dichotomized into “success” and “failure” at Week 4, 8 and 12 with a subject considered a success for those visits if the Global Severity Score is at least 2 grades less than baseline and are Clear or Almost Clear. An additional assessment of subjects who have achieved 2 grade improvement will be also be conducted as a secondary efficacy variable.

The subject will be asked at Baseline and Week 12 to assess how oily their skin has been in the past week.

All assessments will be conducted for both ITT and PP.

12.1 Assessment of Efficacy

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

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
- Proportion of subjects who have a least a 2 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

There are two Week 12 secondary efficacy endpoints:

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

12.1.3 Supportive Efficacy

There is one Week 12 supportive efficacy endpoint:

- Proportion of subjects who have at least a 2 grade reduction at Week 12 from baseline in the Evaluator's Global Severity Score

There are three Week 8 supportive efficacy endpoints:

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

There are three Week 4 supportive efficacy endpoints:

- Percent change in inflammatory lesion count from baseline to Week 4
- Percent change in non-inflammatory lesion count from baseline to Week 4
- Proportion of subjects who have at least a 2 grade reduction at Week 4 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 12.1.7. 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 Statistical Hypothesis Testing and Control of Multiplicity

Statistical hypothesis testing for lesion count analyses will use the statistical model introduced in Section 12.1.3 and employs the methods of Section regarding missing values. The analysis of the dichotomized Evaluator's Global Severity Score will be based on the logistic regression test stratified by analysis center and employs the methods of Section 12.1.7 regarding missing values.

The overall Type I error will be controlled by requiring the co-primary efficacy endpoints of each group 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

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 8
2	Percent change in inflammatory lesion count from baseline to Week 8
3	Percent change in non-inflammatory lesion count from baseline to Week 4
4	Percent change in inflammatory lesion count from baseline to Week 4
5	Proportion of subjects who have at least a 2 grade reduction at Week 12 from

	baseline in the Evaluator's Global Severity Score
6	Proportion of subjects who have at least a 2 grade reduction at Week 8 from baseline in the Evaluator's Global Severity Score
7	Proportion of subjects who have at least a 2 grade reduction at Week 4 from baseline in the Evaluator's Global Severity Score

12.1.6 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 4, 8, and 12.
- Frequency and percent distributions of the dichotomized Evaluator's Global Severity Score at Baseline and Weeks 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 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 4, 8, and 12.
- Frequency and percent distributions for the Oily/Shiny assessments at Week 12

Means, standard deviations and frequency counts (rounded to the nearest whole number) will be computed from the multiply imputed MCMC data for the variable.

12.1.7 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 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. 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 active 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 mail effect will be investigated to determine if the main site-to-site variability is such that it could mask the analysis center effects. Thus, if computationally possible, a one-way ANCOVA (for lesion count variables) or a logistic regression analysis (for EGSS) with a factor of site will be conducted prior to pooling. If the data structure interferes with the logistic regression, a descriptive analysis of the site effect will be undertaken. Conclusions appropriate to the findings of this step will be presented.

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 and secondary 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. 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.

12.1.8 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 Markov Chain Monte Carlo (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 4 distinct phases with these principal tasks:

1. Calculated the number of missing values to be estimated by MCMC (nmiss) for 12 week value.
2. 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 x nmiss’ times to generate ‘5 x nmiss’ 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=5xnmiss <options>;
where trtpn=(1, or 2);
mcmc chain=multiple;
var baseline week4 week8 week12;
run;
```

3. For each complete data set, the absolute change in lesion counts for baseline minus the 12 week value will be computed. Each complete data set will be analyzed as specified for the particular analysis.
4. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 4 random seeds will be needed to impute inflammatory lesion counts from 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-121 Lotion: Seed= 1028933764
- Inflammatory Lesion Counts; IDP-121 Vehicle: Seed= 356782065
- Non-Inflammatory Lesion Counts; IDP-121 Lotion: Seed= 1307444541
- Non-Inflammatory Lesion Counts; IDP-121 Vehicle: Seed= 436373460

EGSS Missing Data Imputation

A similar procedure will be used for the analyses based on proportion of EGSS successes wherein the ANCOVA analysis is replaced with a logistic regression analysis. Specifically, missing 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 4 principal tasks:

1. Calculate the number of missing values to be estimated by MCMC (nmiss) for 12 week value.
2. Create a data set, one for each treatment group, of subjects with observed values and those needing estimation by MCMC. The missing EGSS values in each data set will be filled in using the MCMC method '5 x nmiss' times to generate '5 x nmiss' 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=5xnmiss <options>;
  where trtpn=(1, or 2);
  mcmc chain=multiple;
  var baseline week4 week8 week12;
```

run;

3. For each complete data set, the dichotomous success rate (clear or almost clear with a 2-point change from baseline) will be computed. The 12-week estimated global 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-121 Lotion: Seed= 1210644108
- EGSS; IDP-121 Vehicle: Seed= 763715437

12.1.9 Sensitivity Efficacy Analyses

Sensitivity analyses for absolute change in lesion count

The first sensitivity analysis for absolute change in lesion count 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 Statistical Analysis Plan (SAP), the multiple imputation will involve 4 principal tasks:

1. Calculate the number of missing values (nmiss) for absolute change in lesion count.
2. Missing values will be filled in '5 x nmiss' times to generate '5 x nmiss' complete 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-parameteric method.
3. 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.
4. Results from these analyses will be combined into a single inference.

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 4 principal tasks:

1. Calculate the number of missing values (nmiss) for absolute change in lesion count.
2. Missing values will be filled in '5 x nmiss' times to generate '5 x nmiss' complete 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).
3. Each complete data set will be analyzed with a logistic regression a factors of treatment group and analysis center.
4. Results from these analyses will be combined into a single inference.

12.1.10 Subgroup Analyses

Subset analyses will be conducted for the ITT populations for the subgroups baseline global severity, gender, age, ethnicity, race, and geographic location. 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 be include with categories of less than 18, 18 to less than the median age and greater than or equal to the median age. Geographic region will be dichotomized to US and outside US (OUS). 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.

12.2 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 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 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 medication, the action taken regarding study medication usage, the action taken regarding 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, severity, seriousness, and relationship to study medication. 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 medication. 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 proportion 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 medication.

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 Week 12. Shift tables will be presented for changes in safety laboratory values. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment time point will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

12.2.3 Vital Sign Measurements

Changes from Baseline in vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits.

12.2.4 Concomitant Medications

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

12.2.5 Subject Self-Assessments

Subjects will be asked to complete three questionnaires during the study: the Subject Self Assessment scale, the Patient Satisfaction Survey and the Acne-Specific Quality of Life Questionnaire (Appendices 17.3, 17.4 and 17.5). Descriptive statistics will be used to summarize the data reported for each questionnaire. No Inferential analyses will be conducted.

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 both the ITT population and the PP population. 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 not be compared statistically.

12.5 Protocol Deviations

All protocol deviations will be reported to the sponsor and recorded throughout the study. A listing of protocol deviations will be included in the final study report.

12.6 Compliance

No formal evaluations of compliance are planned.

12.7 Interim Analyses

No interim analyses are planned.

12.8 Additional Statistical Considerations

12.8.1 Analysis Populations

Approximately 800 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:

- 400 subjects will be randomized to receive IDP-121 Lotion, once daily application
- 400 subjects will be randomized to receive IDP-121 Vehicle Lotion, once daily application

The ITT population will consist of all randomized subjects who received study medication. The safety population will be comprised of all randomized subjects who are presumed to have used the study medication at least once and who provide at least one post-baseline evaluation.

An intent-to-treat (ITT) analysis will be conducted on all study subjects. 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, with the exception of a discontinuation from the study due to an adverse event related to study treatment or documented lack of treatment effect;
- Missed both the week 4 and week 8 visits;
- 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.

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.

The safety population will be comprised of all randomized subjects who are presumed to have used the study medication at least once and who provide at least one post-baseline evaluation.

12.8.2 Sample Size Determination

These power calculations are based primarily on the observed Week 12 results of the Study 2 in Atralin™ (tretinoin) Gel, 0.05% NDA 022070 application. This study was a two-arm trial of Atralin™ versus its vehicle and is felt to be a relevant study in NDA 022070 for powering the current study. The next three power calculations are constructed from the results of Study 2.

A sample size of 400 per treatment arm has at least 96% power to detect a statistically significant difference with a significance level of 0.05. The estimated absolute change from baseline in

treatment means were 6.5 and 3.5 for Atralin™ versus its vehicle, respectively, with a standard deviation of 11.3.

A sample size of 400 per treatment arm has greater than 99% power to detect a statistically significant difference with a significance level of 0.05 using the estimated absolute change from baseline in treatment means of 17.8 and 9.9 for Atralin™ versus its vehicle, respectively, with a standard deviation of 24.7.

The sample size estimates for the dichotomized EGSS require a substantially larger enrollment in order to achieve a power of at least 90%. The success rates observed in the second Atralin™ study was 23% for Atralin™ and 14% for its vehicle which is a difference of 9%. Approximately 90% power is achieved with sample sizes of 400 per treatment group, respectively, using a 1:1 randomization.

It is noted that the same differential in success rates was observed in Study 1 (Atralin™ (tretinoin) Gel, 0.05% NDA 022070 application). The success rates observed in the first Atralin™ study was 13% for Atralin™ and 4% for its vehicle which is also a difference of 9%. Using these estimates, more than 99% percent power is achieved with sample sizes of 400 per treatment group.

The clinical study will be conducted under a common protocol at each investigational site and every effort will be made to promote consistency in study execution at each investigational site as well as uniform evaluation of the EGSS evaluation for subjects at the various study visits. The experience in clinical trial execution gained during the execution of several acne studies conducted under the guidance of the Sponsor raises the expectation that the differential between the success rates of the two arms will be greater than 9%. Thus, the power of the EGSS is expected to be at least 95% for sample sizes of 400 subjects in each arm.

Individually and collectively the considerations lead to a choice of randomizing 400 subjects per treatment group.

12.8.3 Handling of Missing Data

The method of multiple imputation will be used (see Section 12.1.8).

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.

12.8.5 Multiplicity Issues

Not applicable.

12.8.6 Windowing Rules

The timing of all study visits is relative to Baseline (Day 0). The 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, the role of the study technician, 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 CRFs. The investigator or designee will enter the information required by the protocol into the source documents and CRFs provided by the sponsor or designee. Subjects will be identified in the CRFs by their assigned subject number and initials only.

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

14 Ethics and Administrative Issues

14.1 Ethical Conduct of the Study

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

14.2 Ethics Review

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. 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 (ie, 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 (eg, laboratory tests). All required data should be recorded in the study documentation completely for prompt data review. Upon study completion or at any other time specified by the sponsor or designee, the appropriate study documents must be submitted.

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

- A statement indicating that the subject has been enrolled in the study and the subject number
- Date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (eg, medical history, screening evaluations)

- Dates of all study related visits and results of any evaluations/procedures performed, including who performed each assessment at each visit
- Use of any concurrent medications during the study
- Documentation of study drug accountability
- Any and all side effects and AEs must be thoroughly documented to conclusion
- Results of any diagnostic tests conducted during the study
- The date the subject exited the study and a statement indicating that the subject completed the study or was discontinued early, including the reason for discontinuation

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

15.2 Retention of Records

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

The investigator will allow representatives of the sponsor's monitoring team, the governing IRB/IEC, the FDA, and other applicable regulatory agencies to inspect all study records, CRFs, 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 CRF, and compliance with FDA or other regulatory agency regulations.

16 References

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17 Appendices

17.1 Subject Instruction Sheet

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

A thin coating of test material should be applied once daily (about the same time every day) to the entire face for twelve weeks. Use the tube to dispense a pea-sized amount of study drug to your fingertip.

This dose should then be dotted on to 6 areas (chin, left cheek, right cheek, nose, left forehead, right forehead) on the face. After distributing the dose in this manner, gently rub the lotion into the skin. This amount should be used to evenly cover the entire face excluding the mouth, eyes and lips. It is important to treat your entire face.

Do NOT treat only specific lesions. DO NOT APPLY MORE THAN THE PRESCRIBED AMOUNT.

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

Reminders:
- On study visit days please wait until after your study visit to apply the study medication.
- Avoid contact with the eyes, inside the nose, mouth and all mucous membranes.
- 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 permitted between 15°C to 30°C (59°F to 86°F). Do not freeze. Avoid excessive heat or cold.
- Tubes of test material must be returned to the study facility, even if they are empty.
- If you miss any doses, at your next visit inform the study doctor of the date(s) of the missed dose(s).
- Continue to use the same, study doctor approved, cleanser, moisturizer and sunscreen throughout the study.
- You must not use any other treatment for your facial acne while you are participating in this study.
- Avoid unnecessary sun exposure and tanning booths.

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

Approved Cleanser Examples:

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

Approved Moisturizer Examples:

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

Approved Moisturizer/Sunscreen Combination Product Examples:

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

17.3 Subject Self Assessment Scoring Scale

Baseline Subject Question

How would rate the current severity of your facial acne condition on a scale of 1-7?

(Check only one box)

☐ 1, Clear or almost clear skin (>90%);

☐ 2, Moderately clear skin (>80% but ≤ 90%);

☐ 3, Fairly clear skin (>70% but ≤ 80%);

☐ 4, Acne covered about 50% of the face;

☐ 5, Fairly severe acne (>70% but ≤ 80% coverage);

☐ 6, Moderately severe acne (>80% but ≤ 90% coverage);

☐ 7, Severe acne, with almost total coverage (>90%).

Week 2 (at-home), 4, 8, and 12 Subject Question

How would rate the current severity of your facial acne condition on a scale of 1-7?

(Check only one box)

☐ 1, clear (100%);

☐ 2, almost clear (90% to <100%);

☐ 3, marked improvement (75% to <90%);

☐ 4, moderate improvement (50% to <75%);

☐ 5, fair improvement (25% to <50%);

☐ 6, no change;

☐ 7, worse

17.4 Patient Satisfaction Survey (PSS)

Baseline Question

On a scale of 1-10 with 1 being the least satisfied and 10 being the most satisfied please rate your level of satisfaction with your prior facial acne therapy.

_____

Week 12 Question

On a scale of 1-10 with 1 being the least satisfied and 10 being the most satisfied please rate your level of satisfaction with your current facial acne study treatment.

_____

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

1. In the past WEEK, how unattractive did you feel because of your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

2. In the past WEEK, how embarrassed did you feel because of your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

3. In the past WEEK, how self-conscious (uneasy about oneself) did you feel about your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

4. In the past WEEK, how upset were you about having facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

5. In the past WEEK, how annoyed did you feel at having to spend time every day cleaning and treating your face because of your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

6. In the past WEEK, how dissatisfied with your self-appearance did you feel because of your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

7. In the past WEEK, how concerned or worried were you about not looking your best because of your facial acne?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

8. In the past WEEK, how concerned or worried were you that your acne medication products were working fast enough in clearing up the acne on your face?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

9. In the past WEEK, how bothered did you feel about the need to always have medication or cover-up available for the acne on your face?

   ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

10. In the past WEEK, how much was your self-confidence (sure of yourself) negatively affected because of your facial acne?

    ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

11. In the past WEEK, how concerned or worried were you about meeting new people because of your facial acne?

    ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

12. In the past WEEK, how concerned or worried were you about going out in public because of your facial acne?

    ☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

13. In the past WEEK, how much was socializing with people a problem for you because of your facial acne?

☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

14. In the past WEEK, how much was interacting with the opposite sex (or same sex if gay or lesbian) a problem for you because of your facial acne?

☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

15. In the past WEEK, how many bumps did you have on your face?

☐Extensive ☐A whole lot ☐A lot ☐A moderate amount ☐Some ☐Very few ☐None

16. In the past WEEK, how many bumps full of pus did you have on your face?

☐Extensive ☐A whole lot ☐A lot ☐A moderate amount ☐Some ☐Very few ☐None

17. In the past WEEK, how much scabbing from your facial acne did you have?

☐Extensive ☐A whole lot ☐A lot ☐A moderate amount ☐Some ☐Very few ☐None

18. In the past WEEK, how concerned or worried were you about scarring from your facial acne?

☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

19. In the past WEEK, how oily was your facial skin?

☐extremely ☐very much ☐quite a bit ☐a good bit ☐somewhat ☐a little bit ☐not at all

Fecha: _____

Cuestionario sobre la calidad de vida, específico al acné

No. de Identificación: ☐

(Favor de marcar una casilla para cada pregunta)

1. Durante la SEMANA pasada, ¿qué tan **poco atractivo(a)** te sentiste debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

2. Durante la SEMANA pasada, ¿qué tan **avergonzado(a)** te sentiste debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

3. Durante la SEMANA pasada, ¿qué tan **acomplejado(a),** [incómodo(a) contigo mismo(a)], te sentiste debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

4. Durante la SEMANA pasada, ¿qué tan **disgustado(a)** te sentiste por tener acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

5. Durante la SEMANA pasada, ¿qué tan **molesto(a)** te sentiste por tomar tanto tiempo diariamente limpiándote y tratándote la cara, debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

6. Durante la SEMANA pasada, ¿qué tan **insatisfecho(a)** te sentiste con tu aspecto personal, debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

7. Durante la SEMANA pasada, ¿qué tan **intranquilo(a) o preocupado(a)** estuviste de no verte lo mejor posible, debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

(Favor de marcar una casilla para cada pregunta)

8. Durante la SEMANA pasada, ¿qué tan **intranquilo(a) o preocupado(a)** estuviste de que los medicamentos y productos para el acné estuviesen funcionando lo suficientemente rápido para eliminar el acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

9. Durante la SEMANA pasada, ¿qué tan **molesto(a)** te sentiste por la necesidad de tener siempre disponibles medicamentos o cremas para cubrir el acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

10. Durante la SEMANA pasada, ¿qué tan **negativo** fue el efecto del acné en tu confianza en ti mismo(a)?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

11. Durante la SEMANA pasada, ¿qué tan **intranquilo(a) o preocupado(a)** te sentiste al conocer a nuevas personas, debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

12. Durante la SEMANA pasada, ¿qué tan **intranquilo(a) o preocupado(a)** te sentiste al salir y estar entre la gente, debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

13. Durante la SEMANA pasada, **¿qué tan problemático fue para ti socializar con las personas,** debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

14. Durante la SEMANA pasada, **¿qué tan problemático fue para ti relacionarte con personas del sexo opuesto** (o del mismo sexo, para homosexuales), debido al acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

(Favor de marcar una casilla para cada pregunta)

15. Durante la SEMANA pasada, ¿cuántos **granos** tenías en la cara?

abundantes	una gran cantidad	muchos	una cantidad moderada	algunos	muy pocos	ninguno
☐	☐	☐	☐	☐	☐	☐

16. Durante la SEMANA pasada, ¿cuántos **granos infectados** tenías en la cara?

abundantes	una gran cantidad	muchos	una cantidad moderada	algunos	muy pocos	ninguno
☐	☐	☐	☐	☐	☐	☐

17. Durante la SEMANA pasada, ¿cuántas **costras o postillas (espinillas secas)** tenías, debido al acné de la cara?

abundantes	una gran cantidad	muchas	una cantidad moderada	algunas	muy pocas	ninguna
☐	☐	☐	☐	☐	☐	☐

18. Durante la SEMANA pasada, ¿qué tan **intranquilo(a) o preocupado(a)** estuviste por las marcas y o cicatrices, que quedaron del acné de la cara?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐

19. Durante la SEMANA pasada, ¿qué tan **grasoso** estaba el cutis?

demasiado	mucho	muy	bastante	algo	un poco	nada
☐	☐	☐	☐	☐	☐	☐