STUDY SYNOPSIS

Title of Study: A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, PARALLEL-GROUP STUDY, COMPARING TEST TOPICAL PRODUCT TO BRAND TOPICAL PRODUCT AND BOTH ACTIVE TREATMENTS TO A PLACEBO CONTROL IN THE TREATMENT OF ACNE VULGARIS

Treatment Duration: The study treatment period will last for 84 days (12 weeks). A window ± 4 days will be considered acceptable for each scheduled visit following the first visit. Expected study duration is 6 to 9 months.

Test Product: Test topical product

Reference Product: Brand topical product

Placebo Control: Vehicle of the test topical product

Dose and Mode of Administration: A thin layer of study medication, approximately a pea-sized amount will be applied to cover the entire face once daily.

Objectives: To evaluate the therapeutic equivalence and safety of Test topical product and Brand topical product in the treatment of acne vulgaris.

To demonstrate the superiority of the efficacy of the test and reference products over that of the placebo control in the treatment of acne vulgaris

Design: Subjects in this randomized, double-blind, placebo controlled, parallel-group, multiple-center study will be randomly assigned in a 1:1:1 ratio to treatment with the test product, reference product or placebo control, respectively.

Clinical Evaluations will be performed at:

Visit 1: Screening/Baseline Visit (Day 0);
Visit 2: First Interim Visit (Week 4 / Day 28 ± 4 Days);
Visit 3: Second Interim Visit (Week 8 / Day 56 ± 4 Days);
Visit 4: End of Treatment Visit (Week 12 / Day 84 ± 4 Days)

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 4 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures will be performed and treated as an interim visit, with the exception of the collection of Investigational Product and Subject diaries from Subjects.

Subjects will be admitted into the study after informed consent/assent has been obtained, a medical history and physical examination (with vital signs) have been

performed and inclusion/exclusion criteria have been met. Subjects must have a clinical diagnosis of acne vulgaris to qualify for inclusion in this study.

Each Subject will be randomly assigned in a double-blind fashion in a 1:1:1 ratio to treatment with the test product, the reference product or the placebo control.

At the screening/baseline visit, a physical examination (with vital signs) will be conducted. At each subsequent visit, the following procedures will be performed: counts of the facial comedones (open and closed), papules, pustules, nodules and cysts lesions will be performed, the Investigator's Global Evaluation (IGA) will be performed and the signs and symptoms of irritation will be assessed.

Safety will be assessed by the monitoring of all adverse events and the monitoring of any signs and symptoms of local irritation.

Study Population:

Inclusion Criteria

1. Healthy male or non pregnant female aged ≥ 12 and ≤ 40 years with a clinical diagnosis of acne vulgaris.

2. Subjects who are 18 years of age or older (up to the age of 40) must have provided IRB approved written informed consent. Subjects 12 to 17 years of age inclusive must have provided IRB approved written assent; this written assent must be accompanied by an IRB approved written informed consent from the Subject's legally acceptable representative (i.e., parent or guardian). In addition, all Subjects or their legally acceptable representatives (i.e., parent or guardian) must sign a HIPAA authorization.

3. Subjects must have a minimum ≥ 25 non-inflammatory lesions (i.e., open and closed comedones) AND ≥ 20 inflammatory lesions (i.e., papules and pustules) AND ≤ 2 nodulocystic lesions (i.e., nodules and cysts), at baseline on the face. For the purposes of study treatment and evaluation, these lesions should be limited to the facial treatment area. All lesions will be counted, including those present on the nose. Subjects may have acne lesions on other areas of the body which will also be excluded from the count, treatment, and the Investigator's Global Assessment (IGA) evaluation (e.g., on the back, chest and arms).

4. Subjects must have a definite clinical diagnosis of acne vulgaris severity grade 2, 3, or 4 as per the Investigator's Global Assessment (IGA) (per Table 1 below).

5. Subjects must be willing to refrain from using all other topical acne medications or antibiotics for acne vulgaris during the 12-week treatment period, other than the investigational product.

6. Female Subjects of childbearing potential (excluding women who are or premenarchal, surgically sterilized or postmenopausal for at least 1 year), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (stabilized for at least 3 months), NuvaRing® (vaginal

contraceptive), Implanon™ (contraceptive implant), double barrier methods (e.g. condom and spermicide), IUD, or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. A sterile sexual partner is NOT considered an adequate form of birth control.

7. All male Subjects must agree to use accepted methods of birth control with their partners, from the day of the first dose administration to 30 days after the last administration of study drug. Abstinence is an acceptable method of birth control. Female partners should use an acceptable method of birth control as described in the above Item Number 6.

8. Subjects must be willing and able to understand and comply with the requirements of the protocol, including attendance at the required study visits.

9. Subjects must be in good health and free from any clinically significant disease, including but not limited to, conditions that may interfere with the evaluation of acne vulgaris. Such conditions include, but are not limited to the following: auto immune disease; rosacea; seborrheic dermatitis; perioral dermatitis; corticosteroid-induced acne; carcinoid syndrome; mastocytosis; acneiform eruptions caused by make-up, medication, facial psoriasis and facial eczema.

10. Subjects who use make-up must have used the same brands/types of make-up for a minimum period of 14 days prior to study entry and must agree to not change make-up brand/type or frequency of use throughout the study.

Table 1: Investigator's Global Assessment (IGA) Scale for Acne Vulgaris

Grade	Description
0	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions

* The eCRF for acne studies will allow for reporting by Investigators of lesion worsening beyond Grade 4 with treatment. It is recommended to not enroll acne vulgaris Subjects with nodulocystic acne. Subjects who worsen beyond Grade 4 will be described in the safety evaluation.

Please note that nodulocystic lesions will not be included in the inflammatory lesion count. Counts of nodules and cysts should be reported separately and not included in the inflammatory or non-inflammatory lesion counts.

Exclusion Criteria

1. Female Subjects who are pregnant, nursing or planning to become pregnant during study participation.

2. Subjects with a history of hypersensitivity or allergy to any of the study medication ingredients and its excipients.

3. Subjects with the presence of any skin condition that would interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneiform eruptions caused by medications, steroid acne, steroid folliculitis, or bacterial folliculitis).

4. Subjects with excessive facial hair (e.g. beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of acne vulgaris.

5. Subjects who have performed wax depilation of the face within 14 days prior to baseline.

6. Subjects who have used within 6 months prior to baseline or use during the study of antiandrogens such as Spironolactone, oral retinoids (e.g. Accutane®), or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).

7. Subjects who have used estrogens or oral contraceptives for less than 3 months prior to baseline; use of such therapy must remain constant throughout the study.

8. Subjects who have used any of the following procedures on the face within 1 month prior to baseline or use during the study:

    a. cryodestruction or chemodestruction,
    b. dermabrasion,
    c. photodynamic therapy,
    d. acne surgery,
    e. intralesional steroids, or
    f. X-ray therapy.

9. Subjects who have used any of the following treatments within 1 month prior to baseline or during the study :

    a. systemic steroids,
    b. systemic antibiotics (except penicillins),
    c. systemic treatment for acne vulgaris, or
    d. systemic anti-inflammatory agents. If Subject uses a systemic anti-inflammatory product during the study, the Principal Investigator will judge if this protocol violation is clinically significant
    e. have taken any drugs that lower your immune system.

10. Subjects who have used any of the following treatments within 2 weeks prior to baseline or during the study:
    a. topical steroids,
    b. topical retinoids,
    c. topical acne treatments including over-the-counter preparations and medicated soaps,
    d. topical anti-inflammatory agents, or
    e. topical antibiotics.

11. Subjects who have received radiation therapy and/or anti-neoplastic agents within 90 days prior to baseline.

12. Subjects who have unstable medical disorders that are clinically significant or have life-threatening diseases.

13. Subjects who have on-going malignancies requiring systemic treatment will be excluded from study participation. In addition, Subjects who have any malignancy of the skin of the facial area will also be excluded.

14. Subjects who engage in activities that involve excessive or prolonged exposure to sunlight or weather extremes, such as wind or cold.

15. Subjects who consume excessive amounts of alcohol (greater than two drinks per day) or use drugs of abuse (including, but not limited to, cannabinoids, cocaine and barbiturates).

16. Subjects who have participated in an investigational drug study (i.e., Subjects have been treated with an investigational drug) within 30 days prior to baseline will be excluded from study participation. Subjects who are participating in non-treatment studies such as observational studies or registry studies can be considered for inclusion.

17. Subjects who have been previously enrolled in this study.

18. Subjects who have had laser therapy, electrodessication and phototherapy (e.g., ClearLight®) to the facial area within 180 days prior to study entry.

19. Subjects who have had cosmetic procedures (e.g., facials) which may affect the efficacy and safety profile of the investigational product within 14 days prior to study entry. Cosmetic procedures and facials are prohibited throughout the study

20. Subjects who currently have or have recently had bacterial folliculitis on the face.

21. Subjects with a baseline irritation score of 3 = severe (marked, intense).

Number of Subjects:

Approximately 1400 Subjects will be enrolled into the study to the following study arms:

- **Test Product**: Test topical product
- **Reference Product**: Brand topical product
- **Placebo Control**: Vehicle of the test topical product

Each site will enroll approximately between 30 and 200 subjects. Approximately equal numbers of male and female subjects will be enrolled to each of the three study arms.

Criteria for Evaluation:

Primary Endpoints:

1) Percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts and;

2) Percent change from baseline to week 12 in the non-inflammatory (open and closed comedones) lesion counts.

Secondary Endpoint:

The proportion of Subjects with a clinical response (IGA) of "success" at week 12. Success should be defined as an IGA score that is at least 2 grades less than the baseline assessment.

Measures[1]:

Lesion Counts will be performed using the following definitions:

- Closed comedone: white, raised bumps caused by collections of oil and skin in pores. Also known as white heads and pimples.
- Open comedone: tiny, dark spots caused by a small plug in the opening of a follicle (pore) on the skin. Also known as blackheads.
- Papule: A papule is solid, raised spot on the skin that is less than 1 centimeter wide.
- Pustule: small, inflamed, pus-filled, blister-like lesions on the skin surface.
- Nodules: Large, hard bumps under the skin's surface
- Cysts: a closed pocket or pouch of tissue. It can be filled with air, fluid, pus, or other material.

The Investigator's Global Assessment (IGA) will be performed and documented using the definitions in Table 1 (above).

Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching will be recorded at each visit to allow a comparison between treatment groups. A detailed scale is presented in Section 5.5.

[1] http://www.nlm.nih.gov/medlineplus/ency/encyclopedia_C.htm

Statistical Methods:

Demonstration of Bioequivalence
Bioequivalence will be established if the 90% confidence intervals of the test/reference ratio of the mean percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts and in the non-inflammatory (comedones) lesion counts are contained within [0.80, 1.25] using the per protocol (PP) population.

Demonstration of Superiority
The test product and RLD will be compared to placebo group to test statistical superiority at $p<0.05$ (two-sided test) with regard to:

1) percent change from baseline to week 12 in the inflammatory lesion counts and 2) percent change from baseline to week 12 in the non-inflammatory lesion counts, both using the modified intent-to-treat (mITT) study population and Last Observation Carried Forward (LOCF).

Analysis of Primary Endpoint
The evaluation of the primary endpoint will be based on the mean percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts and in the non-inflammatory (open and closed comedones) lesion counts.

Analysis of Secondary Endpoint
The secondary endpoint will be evaluated as the proportion of Subjects with a clinical response of “success” at week 12. Success should be defined as an IGA score that is at least 2 grades less than the baseline assessment. Failure is defined as an IGA score that is the same, higher or one grade lower than the baseline assessment. The dichotomized global severity scale should be treated as a secondary end point for supportive evidence.

Analysis of application site reactions
A descriptive analysis comparing the application site reactions for each treatment group will be conducted to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.

Summary of Subjects who terminate prematurely
Reasons for premature termination will be summarized by treatment group.

Concomitant medication
The start and stop date of concomitant medication use during the study will be provided in the data set in addition to the reason for the medication use.

Safety Analyses
Safety analyses will be conducted on the safety population. Safety Incidence of all adverse events reported during the study will be summarized using the MedDRA dictionary by treatment group, body system, severity and relationship to study drug.

The report of AEs will include date of onset, description of the AE, and date of resolution. Formal statistical evaluation(s) of the comparability of the two active treatment groups will be conducted with regard to the frequency and severity of any AE that occurs in at least 5% of the Subjects in either active treatment group.

SAFETY AND TOLERABILITY EVALUATIONS

General Safety Evaluations

A complete medical history will be obtained for the Subject's current and past medical conditions. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity, heart attack, stroke, congestive heart failure, kidney disease, auto immune disease and gestational diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal.

Concomitant medications, including the use of sunscreen, in addition to the reason for the medication use, will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

A brief physical examination will be performed at baseline. The physical examination will include, at a minimum, examination of the Subject's general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart, lungs, musculoskeletal system, neurological system, lymph nodes, abdomen and extremities. The Subject's body weight will also be measured while the Subject is lightly clothed (e.g., no coat or shoes).

Physical Examination

The investigator, sub-investigator or appropriately delegated designee, (Physician's Assistant, Advanced Registered Nurse Practitioner, and Registered Nurse as per local regulations) will perform a brief physical examination, prior to the Subject starting study drug.

Vital signs, including blood pressure, pulse rate, respiratory rate and oral body temperature will be documented at Visit 1. Vital signs will be measured after the Subject has rested in a seated position for at least 5 minutes.

The Subject's body weight will also be measured while the Subject is lightly clothed (e.g., no coat or shoes). Height will be measured without shoes.

Pregnancy Test

All female Subjects of childbearing potential will undergo a urine pregnancy test during Visit 1 and at each subsequent study visit. All female Subjects are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized or have been postmenopausal for at least 1 year. Women of childbearing potential, in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (stabilized for at least 3 months), NuvaRing® (vaginal contraceptive), Implanon™ (contraceptive implant), double barrier methods (e.g. condom and spermicide), IUD, or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. A sterile sexual partner is NOT considered an adequate form of birth control.Subjects on hormonal contraception must

be stabilized on the same type for at least three months prior to enrollment in the study and must not change the method during the study. Subjects who had used hormonal contraception and stopped must have stopped no less than three months prior to the study.

Concomitant medications

Concomitant medications, including the use of sunscreen, in addition to the reason for the medication use, will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

A record of concomitant medications taken by the Subject is to be obtained using generic name, if known, with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications taken on a regular basis, including aspirin and acetaminophen, should be recorded.

Signs/Symptoms of Local Irritation

At each study visit, beginning at Visit 1, Subjects will be evaluated for any signs and symptoms of local irritation, including erythema, dryness, burning/stinging, erosion, edema, pain and itching. Baseline values will be used for comparative purposes against the scores documented at subsequent visits for each treatment group. Each Subject will be assigned a severity score by an Investigator based on the scale in Table 2.

Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain, and itching will be recorded at each visit to allow a comparison between treatment groups.

Table 2: Expected Application Site Reactions

Erythema:	Skin reaction erythema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
Dryness:	Skin reaction dryness score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
Burning/stinging:	Skin reaction burning/stinging score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3-severe (marked, intense)
Erosion:	Skin reaction erosion score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
Edema:	Skin reaction edema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
Pain:	Skin reaction pain score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
Itching:	Skin reaction itching score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

Subjects with a baseline irritation score of 3 (severe, marked/intense) will not be enrolled. After baseline, severe irritation (i.e., grade 3, described as severe or marked/intense) that requires treatment will be reported as an adverse event.

Local irritation reactions in the treatment area are common and the Investigator may instruct Subjects to

stop the application of treatment ("rest period") to reduce Subject discomfort and to allow local skin reactions to subside based upon the Investigator's clinical assessment. Treatment should resume as soon as the reaction subsides sufficiently to allow reapplication. The Subject should not miss the scheduled application for more than three (3) consecutive doses. The Subject should not modify or resume the treatment regimen without consultation with the Investigator. The Investigator may make this decision based upon a documented phone consultation or at an unscheduled visit. All dose modifications must be reported on the appropriate Study Medication Log & Dosing Compliance eCRF.

The treatment period should not be extended beyond 12 weeks due to missed doses or rest periods. Subjects whose condition worsens or lesions do not respond to treatment should be re-evaluated by the Investigator and management reconsidered.

Adverse Events

An adverse event is defined as any untoward medical occurrence (sign, symptom or laboratory finding), regardless of severity and whether or not attributed to the investigational product. All adverse events, whether observed by an Investigator or Study Coordinator or reported by the Subject, whether related to study drug or not related to study drug, shall be documented on the eCRF and Subject records, together with details, i.e. date of onset, the duration and intensity of each episode, the action taken, the relationship to the investigational product and the degree of severity, the seriousness and the outcome.

CLINICAL EVALUATIONS

An examination of the Subject's face will be performed at baseline and at each subsequent visit. During the dermatologic examination, evaluations to determine efficacy of treatment will be conducted, including lesion counts and grading of the Subject's facial acne using the criteria outlined in the IGA.

Preferrably a single Investigator (i.e., Principal Investigator or Sub-Investigator) or qualified staff will perform evaluations of efficacy (i.e., lesion counts and IGA) for each Subject at each visit from the beginning to the end of the Subject's participation to maintain consistency; however, only up to two Investigators or qualified staff may perform evaluations of efficacy for a single Subject if necessary. **All efforts should be made to have the same evaluator at Visit 4 as Visit 1.** All Investigators or qualified staff who will perform evaluations of efficacy must attend study-specific training for the conduct of these evaluations (i.e., lesion counts and IGA).

Lesion Counts

At each visit, an Investigator or qualified staff will assess the Subject's facial acne by counting the number of open and closed comedones, pustules, papules and nodulo-cystic lesions from the jaw line to the hairline. All lesions will be counted, including those present on the nose. A papule with a pustule on its apex will be counted as a pustule.

To be included in the study, Subjects must have a minimum ≥ 25 non-inflammatory lesions (i.e., open and closed comedones) AND ≥ 20 inflammatory lesions (i.e., papules and pustules) AND ≤ 2 nodulocystic lesions (i.e., nodules and cysts), at baseline on the face.

Lesion Type	Definition
Closed Comedone	Non-inflammatory lesion; whitehead, skin-colored or slightly inflamed “bump” in the skin
Open Comedone	Non-inflammatory lesion; blackhead, surface of the plugged sebaceous follicle has a blackish appearance
Papule	Inflammatory lesion; a small (≤ 5mm in diameter), solid palpable lesion, usually with inflamed elevation of the skin that does not contain pus
Pustule	Inflammatory lesion; a small (≤ 5mm in diameter), inflamed skin swelling that is filled with pus
Nodules	Large, hard bumps under the skin's surface
Cysts	Similar to a nodule, but is pus-filled, and ≥ 5mm in diameter

Investigator’s Global Assessment

At each visit, including baseline, an Investigator will assess the overall status of the Subject’s face for acne vulgaris using the IGA. The IGA scores for each visit will be documented on the eCRF.
To be included in the study, subjects must have a definite clinical diagnosis of acne vulgaris of severity grade 2, 3, or 4 at baseline. The following scale will be used for the IGA:

Grade	Description
0	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe; greater than Grade 3; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions

* The eCRF for acne studies will allow for reporting of lesion worsening beyond Grade 4 with treatment. Investigators are recommended to not enroll of acne vulgaris Subjects with nodulocystic acne. Subjects who worsen beyond Grade 4 will be described in the safety evaluation.

Please note that nodulocystic lesions will not be included in the inflammatory lesion count.
Counts of nodules and cysts will be reported separately and not included in the inflammatory or non-inflammatory lesion counts.

STUDY VISITS

Study Visit Schedule

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Visit Week	**Week 0**	**Week 4**	**Week 8**	**Week 12**
Visit Day	**Day 0**	**Day 28±4**	**Day 56±4**	**Day 84±4**
Visit Name	**Screening Baseline**	**Interim**	**Interim**	**EOT/UV/ED[1]**
Informed Consent/Assent and HIPAA	X			
Demographics	X			
Medical History	X			
Concomitant Medication	X	X	X	X
Brief Physical Examination including Vital Signs	X			
Urine Pregnancy Test [2]	X	X	X	X
Inclusion/Exclusion Criteria	X			
Local Irritation Assessment	X	X	X	X
Lesion Counts	X	X	X	X
Investigator's Global Assessment (IGA)	X	X	X	X
Randomization	X			
Adverse Event Reporting	X [3]	X	X	X
Investigational Product Dispensing / Diary Dispensing	X	X	X	
Investigational Product Return / Diary Collection		X	X	X [4]
Diary Review		X	X	X
Investigational Product Accountability		X	X	X
Review of Instructions with Subject (including Diary Completion Instructions)		X	X	
Review of Subject Compliance		X	X	X

[1] EOT - End of Treatment, UV - Unscheduled Visit, ED - Early Discontinuation Visit
[2] The urine pregnancy test is to be conducted for women of child-bearing potential. Tubal ligation is not considered equivalent to female sterilization. Women with a history of tubal ligation are still considered females of childbearing potential and must complete a urine pregnancy test.
[3] Any AEs reported after signing Informed Consent should be reported.
[4] Investigational product and Subject Diaries will be collected from patients during Visit 4 (End of Treatment Visit) or the Early Discontinuation Visit.

Visit 1: Baseline (Day 0)

The following procedures will be performed at Visit 1:

1. **Written informed consent/assent will be obtained**. Subjects who are 18 years of age or older (age 40 years of age inclusive) must have provided IRB approved written informed consent. Subjects ages 12 to 17 years of age, inclusive, must have provided IRB approved written assent. Written assent must be accompanied by an IRB approved written informed consent from the Subject's legally acceptable representative (i.e., parent or guardian). Prior to initiating screening for the study, Subjects will be given the approved ICF/assent describing the study and any risks associated with participation. The Subject will be allowed as much time as needed to read and understand the information presented in the consent/assent form. Appropriate study personnel will be available to answer any questions the Subject might have regarding the study or study-related procedures. If the Subject chooses to participate in the study, he or she will be asked to sign and date the consent/assent form and will be provided with a copy for his or her records. In addition, the Principal Investigator or the Principal Investigator's Designee will provide a HIPAA authorization form (if applicable) for the Subject or the Subject's legally acceptable representative (i.e., parent or guardian) to review and sign. Both the ICF/assent and the HIPAA authorization form (if applicable) must be signed by the Subject or the Subject's legally acceptable representative (i.e., parent or guardian) before any protocol assessments can be undertaken.
2. A complete medical history will be obtained for the Subject's current and past medical conditions. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity*, heart attack, stroke, congestive heart failure, kidney disease, and auto immune disease and gestational diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal.

   * Obesity = BMI ≥30 (as defined by Metropolitan Life Insurance Company Chart)
3. Demographics and vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated position for 5 minutes before vital signs are obtained.
4. A brief physical examination, including height (measured in inches) and weight (measured in pounds), will be performed. At a minimum, the physical examination will include the following: assessment of general appearance, skin, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, extremities.
5. A complete list of current and past (within the previous 30 days) concomitant medications will be obtained for each Subject.
6. A urine pregnancy test will be conducted for all females of childbearing potential.
7. Lesion counts will be done by counting the number of facial open and closed comedones, pustules, papules and nodulo-cystic lesions from the jaw line to the hairline. All lesions will be counted, including those present on the nose.
8. The overall status of the Subject's facial acne vulgaris (from the jaw line to the hairline) will be assessed using the IGA.

9. Subjects will be evaluated for any signs and symptoms of facial irritation, including erythema, scaling, dryness, burning and stinging. Each Subject will be assigned a severity score based on the Local Irritation Scale.
10. When the Subject has completed all screening procedures, compliance with the inclusion and exclusion criteria will be reviewed. After the inclusion and exclusion criteria have been confirmed, the Subject will be randomized to a treatment group. The Subject will be assigned a randomization number
11. The following will be dispensed during Visit 1:
    - The investigational product
    - One Dove Beauty Bar
    - One bottle of Solbar Shield Sunscreen SPF 40
    - Two packs of Graham PST Professional Service Towels
    - A diary card to record product use from Visit 1 to Visit 2

    Depending upon the severity of facial irritation and to prevent the side effects, the Investigator may instruct the Subject to use a non-medicated moisturizer. CeraVe® Moisturizing Lotion may be dispensed during Visit 1 for use at the instruction of the Investigator.
12. Randomized Subjects will be instructed on the correct method for the application of the Investigational Product. The first application of the Investigational Product will be performed by the Subject at home. The study restrictions will also be reviewed with the Subject and an instruction sheet will be issued to the Subject.
13. Randomized Subjects will be provided with a diary and instructed how and when to complete the diary. They will be told that they are to document all treatments administered, including the date and all treatments missed. In addition, Subjects will be instructed to document all AEs. Subjects will also be instructed to call the study site if they experience any severe intolerability (i.e., local skin reactions) to Investigational Product.
14. Visit 2 (Day 28 ± 4 days from the date of Visit 1) will be scheduled and the Subject will be instructed to bring all Investigational Product (used, unused, and partially used) and the Subject diary with him or her to this visit.

Visit 2: Interim Visit (Week 4; Day 28 ± 4 Days)

The following procedures will be performed at Visit 2:

1. Lesion counts will be done by counting the number of facial open and closed comedones, pustules, papules and nodulo-cystic lesions from the jaw line to the hairline. All lesions will be counted, including those present on the nose. (See Section 6.1)
2. The overall status of the Subject's facial acne vulgaris (from the jaw line to the hairline) will be assessed using the IGA. (See Section 6.2)
3. Subjects will be evaluated for any signs and symptoms of facial irritation, including erythema, scaling, dryness, burning and stinging. Each Subject will be assigned a severity score based on the Local Irritation Scale. (See Section 5.5)
4. A urine pregnancy test will be conducted for all females of childbearing potential.

5. The occurrence of all AEs will be assessed and documented following procedures in Sections 5.6 and 10.1.
6. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject. The use of moisturizer, including the type and how often it has been used, will be included. c
7. The Subject's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The Subject's diary will be collected and reviewed for completion. A new diary will be issued.
8. Study drug compliance will be performed and the Subject's used Investigational Product will be returned to the third-party drug dispenser.
9. The following will be dispensed during Visit 2:
    - The investigational product
    - A new diary to record product use from Visit 2 to Visit 3
    - One pack of Graham PST Professional Service Towels

    Depending upon the severity of the side effects, the Investigator may instruct the Subject to use a non-medicated moisturizer. If the moisturizer was not dispensed Visit 1, one bottle of CeraVe® Moisturizing Lotion may be dispensed during Visit 2. It is not anticipated that Subjects will require additional supplies during this visit; additional supplies will be dispensed if required.
10. Study instructions will be reviewed with the Subject, including the procedure for application of the Investigational Product. (See Section 8.5)
11. Visit 3 (Day 56 ± 4 days from the date of Visit 1) will be scheduled and the Subject will be instructed to bring all Investigational Product (used, unused and partially used) and the Subject diary with him or her to this visit.

Visit 3: Interim Visit (Week 8; Day 56 ± 4 Days)

The following procedures will be performed at Visit 3:

12. Lesion counts will be done by counting the number of facial open and closed comedones, pustules, papules and nodulo-cystic lesions from the jaw line to the hairline. All lesions will be counted, including those present on the nose.
13. The overall status of the Subject's facial acne vulgaris (from the jaw line to the hairline) will be assessed using the IGA.
14. Subjects will be evaluated for any signs and symptoms of facial irritation, including erythema, scaling, dryness, burning and stinging. Each Subject will be assigned a severity score based on the Local Irritation Scale.
15. A urine pregnancy test will be conducted for all females of childbearing potential.
16. The occurrence of all AEs will be assessed and documented.
17. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject. The use of moisturizer, including the type and how often it has been used, will be included.

18. The Subject's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The Subject's diary will be collected and reviewed for completion. A new diary will be issued.
19. Study drug compliance will be performed and the Subject's used Investigational Product will be returned to the third-party drug dispenser.
20. The following will be dispensed during Visit 3:
    - The investigational product
    - A new diary to record product use from Visit 3 to Visit 4
    - One *Dove*® soap bar
    - One pack of *Graham PST*® professional service towels

    Depending upon the severity of the side effects, the Investigator may instruct the Subject to use a non-medicated moisturizer. If the moisturizer was not dispensed Visit 1, one bottle of CeraVe® Moisturizing Lotion may be dispensed during Visit 3. It is not anticipated that Subjects will require additional supplies during this visit; additional supplies will be dispensed if required.
21. Study instructions will be reviewed with the Subject, including the procedure for application of the Investigational Product.
22. Visit 4 (Day 84 ± 4 days from the date of Visit 1) will be scheduled and the Subject will be instructed to bring all Investigational Product (used, unused and partially used) and the Subject diary with him or her to this visit.

Visit 4: End of Treatment Visit (Week 12; Day 84 ± 4 Days)

The following procedures will be performed at Visit 4:

1. Lesion counts will be done by counting the number of facial open and closed comedones, pustules, papules and nodulo-cystic lesions from the jaw line to the hairline. All lesions will be counted, including those present on the nose.
2. The overall status of the Subject's facial acne vulgaris (from the jaw line to the hairline) will be assessed using the IGA.
3. Subjects will be evaluated for any signs and symptoms of facial irritation, including erythema, scaling, dryness, burning and stinging. Each Subject will be assigned a severity score based on the Local Irritation Scale.
4. A urine pregnancy test will be conducted for all females of childbearing potential.
5. The occurrence of all AEs will be assessed and documented.
6. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject. The use of moisturizer, including the type and how often it has been used, will be included.
7. The Subject's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The Subject's diary will be collected and reviewed for completion.
8. Study drug accountability/compliance will be performed and the Subject's used medication will be collected.

Unscheduled Visits and Early Discontinuation Visit

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If the Unscheduled Visit is due to an AE, the Principal Investigator will determine whether additional visits are needed.

If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 4 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures scheduled for that interim visit will be performed, with the exception of the collection of Investigational Product and Subject diaries from Subjects.

If the Subject's condition has worsened to the degree that it is unsafe for the Subject to continue in the study, the Subject may be discontinued from the study as treatment failure and a standard of care treatment may be advised at the Principal Investigator's discretion.

If needed, the investigational product and additional supplies can be dispensed during the unscheduled visit.