[redacted]

PROTOCOL TITLE

A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, THREE-ARM, PLACEBO CONTROLLED, PARALLEL-DESIGN GROUP STUDY TO EVALUATE THE THERAPEUTIC EQUIVALENCE COMPARING TRIFAROTENE CREAM, 0.005% (TEVA PHARMACEUTICALS, INC. TO AKLIEF ® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA), IN THE TREATMENT OF ACNE VULGARIS

CLINICAL STUDY PROTOCOL

Protocol Number: TRIF-2101

Protocol Version Number: 2.0

Protocol Version Date: 30JUNE2022

Study Sponsor: Teva Pharmaceuticals, Inc.

PROTOCOL APPROVAL

I am aware of, and agree to comply with, all of the procedures contained within this protocol and requirements of applicable regulatory agencies:

Sponsor Representative	Signature/Date
[redacted] Teva Pharmaceuticals, Inc.	[redacted]
Sponsor Representative	Signature/Date
[redacted]	DocuSigned by: [redacted]

[redacted]

[redacted] Teva Pharmaceuticals, Inc.	
Medical Monitor [redacted]	Signature/Date [redacted]
Statistical Consultant [redacted]	Signature/Date [redacted]
CRO Representative [redacted]	Signature/Date [redacted]

[redacted]

CONTACT LIST

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[redacted]

Retention Samples Storage Facility:
[redacted]

Independent Statistical Consultant:
[redacted]

[redacted]

Institutional Review Board (IRB): [redacted]	

PRINCIPAL INVESTIGATOR AGREEMENT

I have carefully read and understand the foregoing protocol A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, THREE-ARM, PLACEBO CONTROLLED, PARALLEL-DESIGN GROUP STUDY, TO EVALUATE THE THERAPEUTIC EQUIVALENCE COMPARING TRIFAROTENE CREAM, 0.005% (TEVA PHARMACEUTICALS, INC.) TO AKLIEF® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA) IN THE TREATMENT OF ACNE VULGARIS and agree it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH guidelines for Good Clinical Practice (GCP), the Code of Federal Regulations, local regulatory and ethical guidelines. I will attempt to complete the study within the time designated.

I will ensure the rights, safety and welfare, of subjects under my care are protected. I will ensure control of the drugs under investigation in this study.

I will provide access to the protocol and all other study-related information supplied by the Sponsor to all personnel who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all Subject information (case report forms, shipment and drug return forms and all other information collected during the study) and drug disposition in accordance with FDA regulations. I agree to retain and maintain strict accountability of the Investigational Medicinal Products supplied to the study site.

I will not enroll any subjects into this study, until IRB/IEC (Independent Review Board/Institutional Ethics Committee) approval and Sponsor's approval are obtained for protocol.

Principal Investigator	Signature/Date

[redacted]

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[redacted]

LIST OF ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
BA	Bioavailability
BE	Bioequivalence
CDSCO	Central Drugs Standard Control Organization
CFR	Code of Federal Regulations
COVID 19	Coronavirus Disease 2019
CRO	Contract Research Organization/Clinical Research Organization
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HEENT	Head, Eyes, Ears, Nose and Throat
HIPAA	Health Insurance Portability and Accountability Act
IAF	Informed Assent Form
ICF	Informed Consent Form
IGA	Investigator's Global Assessment
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine Device
LOCF	Last Observation Carried Forward
LOTE	Lack of Treatment Effect
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the Counter
PP	Per Protocol
RLD	Reference Listed Drug
SMMP	Safety and Medical Monitoring Plan
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2 (COVID)
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
U.S.	United States

[redacted]

STUDY SYNOPSIS

Protocol Number: TRIF-2101

Version and Date of Protocol: Final Version 1.0, Dated 11-MAY-2022

Title of Study: A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, THREE-ARM, PLACEBO CONTROLLED, PARALLEL-DESIGN GROUP STUDY TO EVALUATE THE THERAPEUTIC EQUIVALENCE COMPARING TRIFAROTENE CREAM, 0.005% (TEVA PHARMACEUTICALS, INC.) TO AKLIEF ® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA) IN THE TREATMENT OF ACNE VULGARIS

Sponsor: Teva Pharmaceuticals, Inc. [redacted]

Clinical Research Organization: [redacted]

Treatment Duration: The study treatment period will last for 84 days (12 weeks). A window period [redacted] will be considered acceptable for each scheduled visit following the screening/baseline visit.

Test Product: TRIFAROTENE CREAM, 0.005% (MANUFACTURED BY ACTAVIS LABORATORIES SALT LAKE CITY, UTAH FOR TEVA PHARMACEUTICALS, INC.)

Reference Listed Product: AKLIEF® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA)

Placebo Control: Vehicle cream (MANUFACTURED BY ACTAVIS SALT LAKE CITY, UTAH FOR TEVA PHARMACEUTICALS, INC.)

Study Phase: Bioequivalence (BE) study with clinical endpoint

Study Site(s): This study will be conducted at multiple centers [redacted].

Dose and Mode

[redacted]

of Administration: Subjects will be instructed to apply enough investigational drug product to lightly cover the entire affected areas of the face once daily at bedtime for 84 days [redacted]

Objectives: To evaluate the clinical therapeutic equivalence of TRIFAROTENE CREAM, 0.005% (and the Reference Listed Product, AKLIEF® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA) 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: To compare the safety of Test, Reference, and Placebo treatments in patients with acne vulgaris.

Subjects in this randomized, double-blind, three-arm, placebo controlled, parallel-design, multi-site study will be randomly assigned [redacted] 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 [redacted]);
Visit 3: Second Interim Visit (Week 8 / Day 56 [redacted]);
Visit 4: End of Treatment Visit (Week 12 / Day 84 [redacted])

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 [redacted] to treatment with either the test product, the reference product or the placebo control.

The treatment area of enrolled subjects will be assessed at all clinic visits, including counts of the facial comedones (open and closed), papules, pustules, nodulocystic lesions (nodules and cysts), the Investigator's Global Assessment (IGA) and the signs and symptoms of irritation (application site reaction) will be assessed.

Safety will be assessed by the monitoring of all adverse events, application site reaction assessments; urine pregnancy test (for females of childbearing potential) and physical examinations including vital signs.

[redacted]

Unscheduled Visits are 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 adverse event (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 the Early Discontinuation Visit will be performed.

Study Population:

Inclusion Criteria

1) Male or non-pregnant, non-lactating 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/IEC approved written informed consent. Subjects 12 to 17 years of age inclusive must have provided IRB/IEC approved written assent; this written assent must be accompanied by an IRB/IEC 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 ≥ 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 screening/baseline on the face.
    (a) 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 be excluded from the count 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) at screening/baseline. Acne vulgaris should be stable (for at least 3 months prior to screening), with minimal variation from day to day and within each day, in the opinion of the subject.

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 will allow for reporting by Investigators of lesion worsening beyond Grade 4 with treatment. Acne vulgaris subjects with nodulocystic acne are not to be enrolled in the study. Subjects who worsen beyond Grade 4 will be described in the safety evaluation.

Note: Counts of nodules and cysts will be reported separately and not included in the inflammatory or non-inflammatory lesion counts.

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

6) Female subjects of childbearing potential (*WOCBP) must not be pregnant or lactating at the time of screening/baseline visit as documented by a negative urine pregnancy test with a sensitivity to at least 25 mIU/ml hCG .

*Female subjects of childbearing potential (WOCBP) are defined as sexually mature women without prior hysterectomy, or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for the past 12 or more months are still considered to be of childbearing potential, if the amenorrhea is possibly due to other causes, including prior chemotherapy, anti- estrogens, or ovarian suppression. Postmenopausal women (defined as women who have been amenorrheic for at least 12 consecutive months, in the appropriate age group, without other known or suspected primary cause) or women who have been sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy, or bilateral oophorectomy with surgery at least 4 weeks prior to randomization) are not considered WOCBP. Subjects who have undergone tubal ligation are NOT considered as surgically sterile.

7) Female subjects of childbearing potential 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.

   a) For the purposes of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, medroxyprogesterone acetate (ex. Depo-Provera®) with stabilized use for at least 3 months, vaginal contraceptive (ex. etonogestrel/ethinyl estradiol vaginal ring (ex. NuvaRing®), contraceptive implant with etonogestrel or equivalent, double barrier methods, (e.g. condom and spermicide), intrauterine device (IUD), true abstinence (if in line with subject's lifestyle).

b) If a subject who was abstinent becomes sexually active during the study, a 2nd acceptable method of birth control should be used and documented.

c) 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. A sterile sexual partner is not considered an adequate form of birth control.

8) Female subjects who are premenarchal, surgically sterilized (by *hysterectomy or bilateral oophorectomy) or postmenopausal for at least 1 year (defined as women who have been amenorrheic for at least 12 consecutive months, without other known or suspected primary cause).

9) 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. True abstinence is an acceptable method of birth control if in line with subject's lifestyle. Female partners should use an acceptable method of birth control as described in the above criteria 7.

10) Subjects must be willing and able to understand and comply with the requirements of the protocol, including attendance at all required study visits and refraining from the use of all other topical acne medications or antibiotics during the 12-week treatment period.

11) Subjects must be in good health and free from any clinically significant disease, which may interfere with the evaluation of acne vulgaris or the administration of the investigative product.

12) 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.

Exclusion Criteria

1) Female subjects who are pregnant, lactating or planning to become pregnant during study participation.

2) Subjects with a history of hypersensitivity or allergy to trifarotene, tretinoin, retinoids, or any of the study medication ingredients.

3) Subjects with the presence of any skin condition that would interfere with the diagnosis or assessment of acne vulgaris (such conditions include but are not limited to the following on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneiform eruptions caused by medications, steroid or corticosteroid-induced acne, steroid folliculitis, or bacterial folliculitis, auto-immune disease, perioral dermatitis, carcinoid syndrome, mastocytosis, acneiform eruptions caused by make-up and medication, facial psoriasis and facial eczema).

4) Subjects with nodulocystic acne (> 2 nodules and cysts). [Nodules or cysts defined as; deep-seated in the skin (i.e., centered in the dermis or subcutis) and an inflammatory lesion greater than or equal to 5 mm in diameter], acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.) or acne vulgaris requiring systemic treatment.

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

6) Subjects with tattoos or excessive facial scarring that, in the Investigator's opinion, may interfere with the evaluation of the patient's acne.

7) Subjects who have used within 6 months prior to screening/baseline oral retinoids (e.g., Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed). These treatments with oral retinoids or Vitamin A supplements are prohibited during the study participation.

8) Subjects who have used within 1 month prior to screening/baseline neuromuscular blocking agents or androgen receptor blockers (e.g., spironolactone, Flutamide etc.).

9) Subjects who have had laser therapy, electrodessication phototherapy and or cosmetic procedures (e.g., ClearLight ® BOTOX, Filler, micro needling) to the facial area within 6 months prior to study entry.

10) Subjects who have had facial cosmetic procedures (e.g., facials) or application of cosmetic products (cosmetics, makeup or facial products that have a strong drying or possible interactive effect, particularly preparations containing spices, lime sulfur, resorcinol, or salicylic acid with tretinoin or other retinoids) which may affect the efficacy and safety profile of the investigational product within 2 weeks prior to study entry.

11) Subjects who have received radiation therapy and/or anti-neoplastic agents within 3 months prior to screening/baseline.

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

13) Subjects who have used any of the following procedures on the face within 1 month prior to screening/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.

14) Subjects who have used any of the following treatments within 1 month prior to screening/baseline or during the study:

    a) androgen receptor blockers (e.g., spironolactone, Flutamide etc.)

    b) systemic steroids,

    c) systemic antibiotics,

d) systemic treatment for acne vulgaris (other than oral retinoids, which require a 6-month washout),

e) systemic anti-inflammatory agents. If Subject uses a systemic anti-inflammatory product during the study, the Principal Investigator will judge if this protocol deviation is clinically significant,

f) have taken any drugs that lower the immune system.

g) topical immunomodulators

15) Subjects who have used any of the following treatments within 2 weeks prior to screening/baseline or during the study:

a) topical steroids,

b) topical retinoids,

c) topical acne treatments including over-the-counter preparations

d) topical anti-inflammatory agents

e) topical antibiotics

f) abradants,

g) peels containing glycolic or other acids,

h) washes or soaps, containing glycolic acid,

i) Alpha-hydroxy acids,

j) sulfacetamide sodium,

k) non-mild facial cleansers, moisturizers that contained retinol

l) topical products that contain high amounts of alcohol

m) wax depilation of the face

n) Use of tanning booths

o) The application of alcohol-based toners or any product with high concentrations of alcohol, astringents, medicated topical preparations (prescription and OTC products including those with spices or lime ingredients). or medicated make-up, medicated or harsh soaps, medicated cleansers, and cosmetics that make subject skin dry to the face (products that have a strong drying effect, particularly preparations containing sulfur, resorcinol, or salicylic acid with tretinoin or other retinoids).

16) Subjects who have on-going malignancies requiring systemic treatment or who have any malignancy of the skin of the facial area.

17) Subjects with active facial sunburn or peeling from sunburn.

18) Subjects who engage in activities that involve excessive or prolonged exposure to sunlight or

weather extremes, such as wind or cold. Exposure to excessive UV radiation within 1 week prior to screening/baseline.

19) Subjects who use a sauna within 48 hours prior to screening/baseline.

20) Subjects who have unstable medical disorders that are clinically significant or have life-threatening diseases, or other medical condition (i.e., chronic infectious disease, system disorder, organ disorder, cardiovascular, gastrointestinal, hematological, hepatic, neurological, pancreatic, renal disease, severe psychiatric condition, etc.) that, in the Investigator's opinion, would place the study Subject at undue risk by participation or could jeopardize the integrity of the study evaluations.

21) 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) within one year prior to screening.

22) Subjects, who in the opinion of the Investigator, would be non-compliant with the requirements of the study protocol.

23) Subjects who are unable or unwilling to give informed consent.

24) Subjects who are illiterate.

25) Subjects who have participated in an investigational drug study (i.e., Subjects have been treated with an investigational drug) within 30 days prior to screening/baseline or where sufficient washout period has not been achieved; whichever time period is longer. Subjects who are participating in non-treatment studies such as observational studies or registry studies can be considered for inclusion.

26) Subjects who have been previously enrolled in this study.

27) Subjects who live in the same household with subjects who are participating or have been previously enrolled in this study.

28) The subject is a member of the investigational study staff or a family member of the investigational study staff.

29) Subject having symptoms* of Coronavirus Disease 2019 (COVID-19) within the 10 days prior to screening/baseline/visit 1 or have had close contact with someone with suspected or confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection within 10 days prior to screening/baseline/visit 1 or who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of acquiring SARS-CoV-2 infections.

*Stuffy or runny nose, sore throat, shortness of breath (difficulty breathing), cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, vomiting, diarrhea, loss of sense of taste and smell.

Number of Subjects:

[redacted]

[redacted]

- TRIFAROTENE CREAM, 0.005% (Teva Pharmaceuticals, Inc.)
- AKLIEF® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA)
- Vehicle cream (Teva Pharmaceuticals, Inc.)

Criteria for Evaluation:

Primary Endpoints:

1) Mean percent change from screening/baseline to week 12 in the inflammatory (papules and pustules) lesion counts and;
2) Mean percent change from screening/baseline to week 12 in the non-inflammatory (open and closed comedones) lesion counts.

* Counts of nodules and cysts will be reported separately and not included in the inflammatory or non-inflammatory lesion counts.

Measures:

a) At each visit, beginning at Visit 1, an Investigator will assess the overall status of the Subject's facial acne vulgaris using the Investigator's Global Assessment (IGA) and the inflammatory lesion counts

b) Proportion of patients with a clinical response of "Clinical Success" using the Investigator's Global Assessment (IGA) at Week 12. Success should be defined as an IGA score that is at least 2 grades less than the baseline assessment. Failure should be defined as an IGA score that is the same, higher or one grade lower than the baseline assessment.

c) Local irritation reactions (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.

Statistical Methods:

Analysis of Primary Endpoint

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

Demonstration of Bioequivalence

Bioequivalence will be established if the 90% confidence intervals of the test/reference ratio of the mean percent change from screening/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) mean percent change from screening/baseline to week 12 in the inflammatory lesion counts and

2) mean percent change from screening/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).

- An active treatment will be considered to be superior to the placebo if the difference in the means for the two treatment groups are statistically significant ($p<0.05$) and the active treatment's mean percent reduction from screening/baseline is greater than that for placebo**.**
- Analysis of local irritation reactions (application site reactions).
- A descriptive analysis comparing the local irritation reactions **(application site reactions)** for each treatment group will be conducted to ensure that the test product is similar to the reference product with regard to the expected and unexpected application site reactions.
- Analysis of IGA scores:
    - Descriptive statistics using categorical methods to compare IGA Scores between each treatment group will be conducted and presented. No inferential analyses are planned.
- Summary of Subjects who terminate prematurely.
    - Reasons for premature termination will be summarized by treatment group.
- Concomitant medication.
    - The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g., Day X) of concomitant medication used prior to and during the study will be provided in the data set in addition to the reason for the medication use. It should clearly be noted whether the medication was used prior to screening/baseline visit, during the study, or both.

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 relatedness to treatment, date of onset, description of the AE, severity, action taken, outcome 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.

Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching will be summarized for the safety population by treatment group and study visit using frequencies and percentages of subjects.

[redacted]

1 INTRODUCTION AND BACKGROUND

Acne vulgaris is a disorder of the pilosebaceous unit[1]. Found in greatest concentrations on the face, upper back, shoulders and chest, a pilosebaceous unit is made up of a hair follicle lined with keratinocytes, a sebaceous gland, and a hair. The sebaceous gland produces a substance called sebum. Although sebum normally empties onto the skin's surface through the openings of the follicles, the follicles may become plugged with hair, sebum and keratinocytes, resulting in comedones. Bacteria normally found on the skin may grow in the comedones, resulting in inflammation. Therefore, acne vulgaris is a multi-factorial disease, caused by the interplay of excess sebaceous gland secretion, bacterial growth, keratinization abnormalities, and immune reactivity.

Acne is clinically characterized by the formation of open and closed comedones (non-inflammatory lesions), papules and pustules (inflammatory lesions) and nodulo-cystic lesions. The highest concentration of lesions is often found on the face, shoulders, upper back, and chest. Although acne vulgaris is most common in adolescents and young adults, it can continue to occur in adults older than 50 years of age.

Although the exact mode of action of trifarotene is unknown, current evidence suggests that topical trifarotene decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation[2]. Additionally, trifarotene stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

AKLIEF® (trifarotene) cream, for topical use was approved by the FDA in 2019 as a prescription product for the safe and effective topical therapy for acne vulgaris[3, 4,5]. Teva Pharmaceuticals, Inc. has developed a generic formulation of trifarotene 0.005% cream. The current study is designed to evaluate the safety and efficacy of this new generic formulation[6]. $ Acne is estimated to affect 9.4% of the global population. There is no mortality associated with acne, but there is often significant physical and psychological morbidity, such as permanent scarring, poor self-image, depression, and anxiety.

2 STUDY OBJECTIVES

The objectives of this study are as follows:

- To evaluate the therapeutic equivalence of TRIFAROTENE CREAM, 0.005% (Teva Pharmaceuticals, Inc.) and the Reference Listed Product, AKLIEF® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA) 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.

- Compare the safety of Test, Reference and Placebo treatments in patients with acne vulgaris.

3 STUDY OVERVIEW

Approximately [redacted] will be assigned [redacted] to treatment with the test product, TRIFAROTENE 0.005% CREAM, the reference product, AKLIEF® (TRIFAROTENE 0.005% CREAM, and placebo (vehicle cream of the test product) in this multiple-center, double-blind, randomized, three-arm, placebo controlled, parallel-design study.

The duration of each Subject's participation in the study will be 84 days. Scheduled study visits will include:

- Visit 1 (Day 0) Screening/Baseline
- Visit 2 (First Interim Visit, Day 28)
- Visit 3 (Second Interim Visit, Day 56)
- Visit 4 (End of Treatment/Early Discontinuation Visit, Day 84).

A window period [redacted] will be considered acceptable for each scheduled visit following the screening/baseline visit.

At Visit 1, an informed consent/assent will be obtained from the potential study Subject prior to any study procedures taking place. After the Subject has been consented/assented, the Subject's medical history will then be documented, including the Subject's concomitant medications. A urine pregnancy test with a sensitivity to at least 25 mIU/ml hCG will be performed for female subjects of childbearing potential. A negative result of this test should be obtained.

If necessary, subjects will be allowed to conduct screening procedures on two separate days in order to allow for enough time to complete the adequate washout period required for any concomitant therapy or other reasons. Subjects should sign ICF (prior to the start of any study procedures), complete washout, and return to the clinic to conduct the remainder of the screening/baseline procedures.

The Subject will undergo a physical examination, including the recording of vital signs and COVID-19 symptom (such as stuffy or runny nose, sore throat, shortness of breath (difficulty breathing), cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish (temperature check), vomiting, diarrhea, loss of sense of taste and smell) screening. The Subject will be reviewed against the inclusion/exclusion criteria and a screening/baseline acne grade will be assigned to the Subject using the Investigator's Global Assessment (IGA) and a screening/baseline lesion count will be performed.

The Subject will be evaluated for signs and symptoms of local irritation. Blinded Investigational Medicinal Product (IMP) will be dispensed by Independent Dispenser to subjects who meet all of the inclusion and none of exclusion criteria. Eligible subjects will be assigned to one of the

three study treatment groups as per the computer-generated randomization schedule, and the assigned study medication will be dispensed by the Independent Dispenser. Since this is a double-blind study, neither the study team other than Independent Dispenser at the site nor the subjects will know the treatment the subject is assigned.

Subjects will be instructed by an Independent Dispenser on the application of IMP and completion of Subject diaries. The Independent Dispenser will not be involved in the assessments/evaluations of acne lesion counts, Investigator's Global Assessment (IGA), evaluation of signs and symptoms of local irritation and safety assessments.

The Subject will also be instructed not to open the study medication pump while at the study site. The application of Investigational Medicinal Products will be performed by the Subject at home.

Subjects will be instructed to apply enough study investigational drug to lightly cover the entire affected areas of the face for 84 consecutive days. The IMP should be applied once daily at bedtime after the Subject's face has been washed with a non-medicated cleanser provided by the Sponsor, and gently patted dry. The subjects should wait 20 to 30 minutes before applying the study medication to allow the skin to be completely dry in order to minimize possible irritation. For the purposes of this study, the face is considered to start at the hairline and end at the jaw line and excludes the eyes, the lips/mouth, angles/corners of the nose, open wounds and all mucous membranes.

The subject will be instructed to wash their hands before and after application of study drug.

Subjects will be required to use diaries to document the date and time of study treatments, any missed treatments, any concomitant medication and the occurrence of all adverse events.

The subjects will be instructed to bring their used IMP and their study diaries to each study visit.

Subjects will return to the study site for Visit 2, Visit 3 and Visit 4. The Subject's concomitant medications (if any), IMP compliance and any AEs will be reviewed and documented. A temperature check and COVID-19 symptom (such as stuffy or runny nose, sore throat, shortness of breath (difficulty breathing), cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish (temperature check), vomiting, diarrhea, loss of sense of taste and smell) screening will be performed. A urine pregnancy test with a sensitivity of at least 25 mIU/ml hCG will be performed for female subjects of childbearing potential. A negative result of this test should be obtained.

The Subject will be evaluated for signs and symptoms of local irritation and any adverse events will be documented. The Subject's facial acne will be assessed using the IGA, the Subject's lesions will be counted, and these results will be documented.

If the Principal Investigator determines that 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 a treatment failure and the Subject may be treated using the standard care or rescue medicines if there is exacerbation of their acne.

The subjects are instructed to bring their used IMP and their study diaries to each study visit.

[redacted]

Compliance with drug applications will be assessed at each visit. Additional pumps of IMP will be dispensed at the visit if required, and each Subject will receive new diaries during Visit 2 and Visit 3. In addition, all IMP and diaries will be collected from the Subject during each scheduled visit or the Early Discontinuation Visit.

At every study visit, all the procedures mentioned in the Table of events (Section 4) will be carried out. The treatment area of enrolled subjects will be assessed using IGA and lesion count. Additionally, adverse events (AEs) will be monitored, and the treatment area will be examined to assess application site reactions. Any change in concomitant medications will be noted.

Unscheduled Visits are 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 the Early Discontinuation Visit 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 the reason for the unscheduled visit is documented and required procedures at the discretion of Investigator considering the reason for visit will be performed, with the exception of the collection of IMP and Subject diaries from Subjects.

[redacted]

[redacted]

4 STUDY VISIT SCHEDULE

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Unscheduled / Early Discontinuation
Visit Day	Day 0	Day 28 [redacted]	Day 56 [redacted]	Day 84 [redacted]	
Visit Name	Screening and Baseline	First Interim	Second Interim	End of Treatment	
COVID-19 symptom screening	✓	✓	✓	✓	✓
Informed Consent	✓				
Inclusion / Exclusion Criteria	✓				
Demographics (Date of birth, gender, race and ethnicity)	✓				
Medical History	✓				
Physical Exam	✓			✓	✓ as needed
Vital Signs	✓	✓[3]	✓[3]	✓[3]	✓[3]
Urine Pregnancy Test To be conducted for all women of child-bearing potential[1]	✓	✓	✓	✓	✓
Clinical Assessment of Acne: Investigator's Global Assessment (IGA)	✓	✓	✓	✓	✓
Investigator's Lesion Counts Inflammatory and Non-Inflammatory	✓	✓	✓	✓	✓
Randomization	✓				
Dispense IMP and Supplies	✓	✓[4]	✓[4]		
Dispense Diary /Instructions	✓	✓	✓		
IMP Review and Collection Finished cream pumps of IMP will be returned [4](as necessary)		✓	✓	✓	✓as needed
Subject Compliance/ Diary Review and collection		✓	✓	✓	✓as needed
Evaluation of Signs/Symptoms of Local Irritation (Application Site Reactions)	✓	✓	✓	✓	✓
Adverse Events Assessment[2]	✓	✓	✓	✓	✓
Concomitant Medication Review	✓	✓	✓	✓	✓

[redacted]

[1] 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 have a negative urine pregnancy test with a sensitivity of at least 25 mIU/ml hCG.
[2] Any AEs reported after signing Informed Consent should be reported.
[3] Only Temperature check at visit 2, 3, 4 and Unscheduled / Early Discontinuation as part of COVID-19 symptom screening.
[4]Additional IMP and supplies will be provided to the Subject as required.

5 STUDY POPULATION

5.1 Number of Subjects

This multi-center study will be comprised of subjects presenting with a clinical diagnosis of acne vulgaris who meet all inclusion and none of exclusion criteria. [redacted]

- **TEST:** TRIFAROTENE CREAM, 0.005% (Teva Pharmaceuticals, Inc.)
- **REFERENCE**: AKLIEF® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA)
- **PLACEBO**: Vehicle cream (Teva Pharmaceuticals, Inc.)

Note: Number of study sites [redacted] may vary based on the subject recruitment rate.

5.1.1 Inclusion Criteria

1) Male or non-pregnant, non-lactating 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/IEC approved written informed consent. Subjects 12 to 17 years of age, inclusive, must have provided IRB/IEC approved written assent; this written assent must be accompanied by an IRB/IEC 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 ≥ 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 screening/baseline on the face.

   (a)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 be excluded from the count 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 2 below) at screening/baseline. Acne vulgaris should be stable (for at least 3 months prior to screening), with minimal variation from day to day and within each day, in the opinion of the subject.

Table 2: 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 will allow for reporting by Investigators of lesion worsening beyond Grade 4 with treatment. Acne vulgaris Subjects with nodulocystic acne are not to be enrolled in the study. Subjects who worsen beyond Grade 4 will be described in the safety evaluation.

Note: Counts of nodules and cysts will be reported separately and not included in the inflammatory or non-inflammatory lesion counts.

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

6) Female Subjects of childbearing potential (*WOCBP) must not be pregnant or lactating at the time of screening/baseline visit as documented by a negative urine pregnancy test.

*Female subjects of childbearing potential (WOCBP) are defined as sexually mature women without prior hysterectomy, or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for the past 12 or more months are still considered to be of childbearing potential, if the amenorrhea is possibly due to other causes,

including prior chemotherapy, anti- estrogens, or ovarian suppression. Postmenopausal women (defined as women who have been amenorrheic for at least 12 consecutive months, in the appropriate age group, without other known or suspected primary cause) or women who have been sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy, or bilateral oophorectomy with surgery at least 4 weeks prior to randomization) are not considered WOCBP. Subjects who have undergone tubal ligation are NOT considered as surgically sterile.

7) Female subjects of childbearing potential 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.

   (a) For the purposes of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, medroxyprogesterone acetate (ex. Depo-Provera®) with stabilized use for at least 3 months, vaginal contraceptive (ex. etonogestrel/ethinyl estradiol vaginal ring (ex. NuvaRing®), contraceptive implant with etonogestrel or equivalent, double barrier methods (e.g. condom and spermicide), intrauterine device (IUD), true abstinence (if in line with subject's lifestyle).

   (b) If a subject who was abstinent becomes sexually active during the study, a 2nd acceptable method of birth control is to be used and documented.

   (c) 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. A sterile sexual partner is not considered an adequate form of birth control.

8) Female subjects who are premenarchal, surgically sterilized (by *hysterectomy or bilateral oophorectomy) or postmenopausal for at least 1 year) (defined as women who have been amenorrheic for at least 12 consecutive months, without other known or suspected primary cause).

9) 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. True abstinence is an acceptable method of birth control if in line with subject's lifestyle. Female partners should use an acceptable method of birth control as described in the above criteria.

10) Subjects must be willing and able to understand and comply with the requirements of the protocol, including attendance at all required study visits and refraining from the use of all other topical acne medications or antibiotics during the 12-week treatment period.

11) 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 or the administration of the investigative product.

12) 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.

5.1.2 Exclusion Criteria

1) Female Subjects who are pregnant, lactating or planning to become pregnant during study participation.
2) Subjects with a history of hypersensitivity or allergy to trifarotene, tretinoin, retinoids, or any of the study medication ingredients.
3) Subjects with the presence of any skin condition that would interfere with the diagnosis or assessment of acne vulgaris (Such conditions include but are not limited to the following on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneiform eruptions caused by medications, steroid or corticosteroid-induced acne, steroid folliculitis, or bacterial folliculitis, auto-immune disease, perioral dermatitis, carcinoid syndrome, mastocytosis, or acneiform eruptions caused by make-up and medication, facial psoriasis and facial eczema).
4) Subjects with nodulocystic acne (> 2 nodules and cysts). [Nodules or cysts defined as; deep-seated in the skin (i.e., centered in the dermis or subcutis) and an inflammatory lesion greater than or equal to 5 mm in diameter], acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), or acne vulgaris requiring systemic treatment.
5) Subjects with excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of acne vulgaris.
6) Subjects with tattoos or excessive facial scarring that, in the Investigator's opinion, may interfere with the evaluation of the subject's acne.
7) Subjects who have used within 6 months prior to screening/baseline oral retinoids (e.g., Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed). These treatments with oral retinoids or Vitamin A supplements are prohibited during the study participation.
8) Subjects who have used within 1 month prior to screening/baseline neuromuscular blocking agents or androgen receptor blockers (e.g., spironolactone, Flutamide etc.).
9) Subjects who have had laser therapy, electrodessication, phototherapy and or cosmetic procedures (e.g., ClearLight® BOTOX, Filler, micro needling) to the facial area within 6 months prior to study entry.
10) Subjects who have had facial cosmetic procedures (e.g., facials) or application of cosmetic products (cosmetics, makeup or facial products that have a strong drying or possible interactive effect, particularly preparations containing spices, lime sulfur, resorcinol, or salicylic acid with tretinoin or other retinoids) which may affect the efficacy and safety profile of the IMP within 2 weeks prior to study entry.

11) Subjects who have received radiation therapy and/or anti-neoplastic agents within 3 months prior to screening/baseline.

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

13) Subjects who have used any of the following procedures on the face within 1 month prior to screening/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.

14) Subjects who have used any of the following treatments within 1 month prior to screening/baseline or during the study:

    a. androgen receptor blockers (e.g., spironolactone, Flutamide etc.)

    b. systemic steroids,

    c. systemic antibiotics,

    d. systemic treatment for acne vulgaris (other than oral retinoids, which require a 6-month washout),

    e. systemic anti-inflammatory agents. If Subject uses a systemic anti-inflammatory product during the study, the Principal Investigator will judge if this protocol deviation is clinically significant,

    f. have taken any drugs that lower the immune system

    g. topical immunomodulators

15) Subjects who have used any of the following treatments within 2 weeks prior to screening/baseline or during the study:

    a) topical steroids,

    b) topical retinoids,

    c) topical acne treatments including over-the-counter preparations

    d) topical anti-inflammatory agents

    e) topical antibiotics

    f) abradants,

    g) peels containing glycolic or other acids,

h) washes or soaps, containing glycolic acid,

i) Alpha-hydroxy acids,

j) sulfacetamide sodium,

k) non-mild facial cleansers, moisturizers that contained retinol

l) topical products that contain high amounts of alcohol

m) wax depilation of the face

n) use of tanning booths

o) application to face of alcohol-based toners, cosmetics, makeup or any product with high concentrations of alcohol, astringents, medicated topical preparations (prescription and OTC products including those with spices or lime) or medicated make-up, medicated or harsh soaps, medicated cleansers, and cosmetics that make subject skin dry to the face (products that have a strong drying effect, particularly preparations containing sulfur, resorcinol, or salicylic acid with tretinoin or other retinoids).

16) Subjects who have on-going malignancies requiring systemic treatment or who have any malignancy of the skin of the facial area.

17) Subjects with active facial sunburn or peeling from sunburn.

18) Subjects who engage in activities that involve excessive or prolonged exposure to sunlight or weather extremes, such as wind or cold. Exposure to excessive UV radiation within 1 week prior to screening/baseline.

19) Subjects who use a sauna within 48 hours prior to screening/baseline.

20) Subjects who have unstable medical disorders that are clinically significant or have life-threatening diseases, or other medical condition (i.e., chronic infectious disease, system disorder, organ disorder, cardiovascular, gastrointestinal, hematological, hepatic, neurological, pancreatic, renal disease, severe psychological conditions etc.) that, in the Investigator's opinion, would place the study Subject at undue risk by participation or could jeopardize the integrity of the study evaluations.

21) 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) within one year prior to screening.

22) Subjects, who in the opinion of the Investigator, would be non-compliant with the requirements of the study protocol.

23) Subjects who are unable or unwilling to give informed consent.

24) Subjects who are illiterate.

25) Subjects who have participated in an investigational drug study (i.e., Subjects have been treated with an investigational drug) within 30 days prior to screening/baseline or where

sufficient washout period has not been achieved; whichever time period is longer. Subjects who are participating in non-treatment studies such as observational studies or registry studies can be considered for inclusion.

26) Subjects who have been previously enrolled in this study.

27) Subjects who live in the same household with subjects who are participating or have been previously enrolled in this study.

28) The subject is a member of the investigational study staff or a family member of the investigational study staff.

29) Subject having symptoms* of Coronavirus Disease 2019 (COVID-19) within the 10 days prior to screening/baseline/visit 1 or have had close contact with someone with suspected or confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection within 10 days prior to screening/baseline/visit 1 or who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of acquiring SARS-CoV-2 infections.

a) *Stuffy or runny nose, sore throat, shortness of breath (difficulty breathing), cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, vomiting, diarrhea, loss of sense of taste and smell.

5.1.3 Prohibited Medications, Procedures, and Activities

Medication necessary for the health and well-being of the subject is permitted provided the subject has been at a stable dose for 30 days prior to screening/baseline visit. The use of any medication that could affect the course of acne is prohibited during the entire study period. Subjects should not apply creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. See below Table 3: Restrictions and Prohibited Medications & also exclusion criteria.

[redacted]

[redacted]

Table 3: Restrictions and Prohibited Medications

[redacted]				
[redacted]	[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]				
[redacted]	[redacted]	[redacted]		
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[redacted]

[redacted]

Acceptable Medications for use throughout the study:

1. Contraceptives – Acceptable methods of birth control as listed in the Inclusion Criteria. Subjects on hormonal contraception must be stabilized on the same type for at least 3 months prior to enrollment in the study and must not change the method during the study.
2. Acetaminophen - Acetaminophen will be allowed during the study with a maximum dose of 1g (i.e., 1000 mg) twice daily and for a maximum of 3 consecutive days.
3. Non-medicated moisturizers (supplied by sponsor) or cleaning agents only, when necessary, as directed by investigator.
4. Oral retinoids, therapeutic vitamin A supplements of less than 10,000 units/day (multi-vitamins are allowed).

Subjects will be allowed to apply the study medication to any affected area(s) of their trunk as needed. No other medication will be allowed to be applied to these affected area(s).

Subjects will be questioned about all prescription and over the counter (OTC) concomitant medication use (including vitamins, nutritional supplements, herbal supplements, all topical products) at each study visit. All concomitant medications will be recorded in the Subject's source documents. Any Subject who violates the listed restrictions may be dropped from continued participation in the study by the discretion of investigator.

5.1.4 Precautions

The following precautions are to be taken during this study:

1. To minimize exposure to sunlight and or extreme weather conditions, a wide-brimmed hat or other protective clothing should be worn. [redacted]
2. The IMP should not be applied to cuts, open wounds, abrasions, sunburn or eczematous skin.
3. The IMP should not be applied to the eyes, the mouth/lips, the angles/corners of the nose or any mucous membranes.
4. Subjects should wash their hands before and after application of the product.

If a reaction suggesting sensitivity or chemical irritation occurs, the Principal Investigator should assess the Subject's condition as soon as possible (i.e., during an Unscheduled Visit) and determine whether treatment should be discontinued. 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 the Early Discontinuation Visit will be performed.

[redacted]

5.1.5 Subject Disposition and Discontinuation

All Subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrollment are to be followed explicitly. Investigators are urged to enroll only those eligible Subjects who are likely to complete the entire study and who are willing to comply with the protocol-specified procedures. It is the right and duty of the investigator to interrupt the treatment of any Subject whose health or well-being may be threatened by continuation in this study, or who may be experiencing unmanageable factors that may interfere with the study procedures and/or the interpretation of study results. Such Subjects should be withdrawn from the study rather than continued under a modified regimen. The reason for withdrawal or discontinuation from the study will be documented appropriately.

In addition, investigational product will be stopped, and Subjects will be discontinued from the study for any of the following reasons:

a. If the Subject withdraws his or her consent/assent for any reason.
b. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population as treatment failures, using Last Observation Carried Forward (LOCF).
c. If the Subject's acne condition has worsened beyond grade 4 or to the degree that the Principal Investigator feels it is unsafe for the Subject to continue in the study, the subject should be discontinued, but included in the mITT and PP population analysis using LOCF and provided with effective rescue treatment for exacerbation of their acne.
d. [redacted]
e. If the Subject has a SAE.
f. If the Subject's drug code is unblinded.
g. If an adverse event occurs for which the Subject desires to discontinue treatment or the Principal Investigator determines that it is in the Subject's best interest to be discontinued.
h. If there is a significant protocol deviation if it affects the safety or well-being of the subject.
i. [redacted]
j. If a concomitant therapy is reported or required which is liable to interfere with the results of the study.
k. If the Subject is lost to follow-up.
l. If the Subject becomes pregnant.
m. If the Subject becomes a prisoner or becomes involuntarily incarcerated.
n. Any other reason that may affect the outcome of the study or the safety of Subjects; or
o. Termination of the study by the Sponsor.

Subjects who withdraw from the study early will have Early Discontinuation procedures performed. Subjects who withdraw from the study will not be replaced. All subjects who are randomized will be included in the safety monitoring tabulating all adverse events experienced after dosing.

A significant or major protocol deviation is defined as any subject or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment, safety or well-being of the subject or the precise evaluation of treatment efficacy such as may affect data integrity. Subjects with protocol deviations are not required to be discontinued from the study unless, in the Investigator's opinion, continuation in the study could be harmful to the health or wellbeing of the subject. Subjects that have a major protocol deviation which effects their safety or wellbeing should be discontinued.

The reasons for a Subject discontinuation will be documented. If a Subject is discontinued from the study for any reason, Early Discontinuation Visit procedures will be completed and any outstanding data and study drug should be collected if possible. In addition to the reason for discontinuation the collected data will include the initiation of any rescue medicines, the date of removal and will be documented in the electronic Case Report Form (eCRF). The Sponsor will be notified.

Before a subject is considered to be lost to follow-up, the Principal Investigator will document all attempts to reach the Subject twice by telephone and will send a certified follow-up letter.

In the event that a subject discontinues from the study at any time due to an adverse event (AE), the reason for discontinuation, the nature of the event and its clinical course must be fully documented (see also reporting AEs and SAES, Section 11.0). For such a subject, the Principal Investigator must strive to follow the subject until the adverse event has resolved, becomes clinically insignificant, is stabilized or the subject is lost to follow-up. In case of any serious adverse events, procedures for reporting must be followed.

6 SAFETY AND TOLERABILITY EVALUATIONS

Safety will be assessed based on following:

- Vital signs evaluation,
- Physical Examination
- COVID-19 symptoms screening,
- Reported Adverse Events and Serious Adverse Events,
- Assessment of local facial tolerability-rating of erythema, dryness, stinging/burning, erosion, edema, pain and itching for each treatment group will be recorded and reported,
- Lack of effect of investigative products on indication.

[redacted]

6.1 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[1], 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 and treatments, including the use of sunscreen, OTC products, herbal products, topical and systemic medicines, (non-drug treatments/therapies) etc., in addition to the reason for the medication use, will be assessed at screening/baseline and at each subsequent study visit. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g., Day X) and name of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. It should clearly be noted whether the medication was used prior to screening/baseline visit, during the study, or both.

Additional assessment to assess subject safety, such as physical examinations, measurements of vital signs are described below and included in the Schedule of Assessments for periodic measurements.

All female subjects of childbearing potential will undergo a urine pregnancy test with a sensitivity of at least 25 mIU/ml hCG at Visit 1, Visit 2, Visit 3 and Visit 4. A negative result of urine pregnancy test at visit 1, 2, 3 and 4 should be obtained. All female subjects are considered to be of childbearing potential unless they are premenarchal or have been surgically sterilized or have been postmenopausal for at least 1 year.

6.1.1 Physical Examination

A brief physical examination will be performed at screening/baseline, Visit 4 End of Treatment/Early Discontinuation and during an UNS visit where applicable. 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. It is recommended the Subject's body weight should be measured while the Subject is lightly clothed (e.g., no coat or shoes).

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. A delegation log will be maintained at site.

[1] Obesity = BMI ≥30 (as defined by Metropolitan Life Insurance Company Chart, Appendix III)

[redacted]

6.1.2 Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate and body temperature will be documented at Visit 1, Visit 2, Visit 3 and Visit 4. Vital signs will be measured after the subject has rested in a seated position for about 5 minutes.

Blood pressure (millimeters of mercury [mmHg]) and heart rate (beats per minute [bpm]) will be measured during the physical examination after 5 minutes rest in sitting position. Blood pressure and heart rate will be obtained preferably using the same arm and same equipment each time. If one arm has higher blood pressure than the other, that arm should be used for further blood pressure measurements (all further blood pressure measurements should be done in the same arm).

Body temperature will be measured using FDA approved tympanic or infrared thermometer with digital display and recorded in the eCRF in degree Celsius (°C). Preferably the same method will be used each time.

Vital signs, including blood pressure, pulse rate, respiratory rate and 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. Additionally, temperature will also be documented at Visit 2, 3, 4 and Unscheduled / Early Discontinuation as part of COVID-19 symptom screening.

6.1.3 Pregnancy Test

All female Subjects of childbearing potential will undergo a urine pregnancy test with a sensitivity of at least 25 mIU/ml hCG 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 (by *hysterectomy or bilateral oophorectomy) or have been postmenopausal for at least 1 year. Tubal ligation is not considered equivalent to female sterilization. Women with a history of tubal ligation are still considered females able to become pregnant and must complete a urine pregnancy test.

*Female subjects of childbearing potential (WOCBP) are defined as sexually mature women without prior hysterectomy, or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for the past 12 or more months are still considered to be of childbearing potential, if the amenorrhea is possibly due to other causes, including prior chemotherapy, anti- estrogens, or ovarian suppression. Postmenopausal women (defined as women who have been amenorrheic for at least 12 consecutive months, in the appropriate age group, without other known or suspected primary cause) or women who have been sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy, or bilateral oophorectomy with surgery at least 4 weeks prior to randomization) are not considered WOCBP. Subjects who have undergone tubal ligation are NOT considered as surgically sterile.

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.

Female subjects who are premenarchal, surgically sterilized (by hysterectomy or bilateral oophorectomy) or postmenopausal for at least 1 year, do not require a urine pregnancy test and are not required to use an acceptable form of birth control.

Full hysterectomy or bilateral oophorectomy are considered surgically sterile. Tubal ligation is not considered equivalent to female sterilization.

For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, medroxyprogesterone acetate (ex. Depo-Provera®) with stabilized use for at least 3 months, vaginal contraceptive (ex. etonogestrel/ethinyl estradiol vaginal ring (ex. NuvaRing®), contraceptive implant with etonogestrel or equivalent, double barrier methods (e.g., condom and spermicide), IUD, abstinence. If a subject who was abstinent becomes sexually active during the study, a 2nd acceptable method of birth control should be used and documented.

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.

6.2 Concomitant Medications

Concomitant medications and therapeutic treatments, including the use of sunscreen, OTC products, herbal products, topical and systemic medicines, dietary supplements and any current non-drug treatments/therapies will be assessed at the screening/baseline visit and at each subsequent study visit. The start and stop calendar date (e.g., dd/mmm/yyyy and study day (e.g., Day X) of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication or treatment use. It should clearly be noted whether the medication was used prior to screening/baseline visit, during the study, or both.

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. Any therapeutic treatments during the trial should also be recorded. All medications taken on a regular basis, including acetaminophen, should be recorded.

6.3 Evaluation of Signs/Symptoms of Local Irritation/Application Site Reactions

At each study visit, beginning at Visit 1, Subjects will be evaluated for any signs and symptoms of local irritation such as erythema, dryness, burning/stinging, erosion, edema, pain and itching. The scores for each visit will be documented to allow a comparison between treatment groups.

The following scale will be used for the signs and symptoms of local irritation:

Score	Assessment	Description
0	Absent	None
1	Mild	Slight, barely perceptible
2	Moderate	Distinct presence
3	Severe	Marked, intense

Subjects with a screening/baseline irritation score of 3 (severe, marked/intense) will not be enrolled.

Signs and symptoms of local irritation are to be recorded only as AEs if they significantly worsen, require any medical intervention or result in subject discontinuation (eg. after screening/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. The Investigator may advise the subject to use the Sponsor provided moisturizer at this time. Treatment should resume as soon as the reaction subsides sufficiently to allow reapplication. The [redacted]. 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, along with Subject documenting in the subject diary.

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 following at least 28 days (or in the opinion of the Investigator) should be re-evaluated by the Investigator and management reconsidered.

6.4 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence (sign, symptom or abnormal laboratory finding) regardless of severity in a Subject or clinical-trial Subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. 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 Subject records, together with details, i.e., date of onset,

description of the AE, the duration and intensity of each episode, the action taken, the relationship to the IMP and the degree of severity, the seriousness, date of resolution and the outcome.

All reported adverse events and serious adverse events will be recorded and reported as per section 11.0 Adverse Events.

6.5 COVID-19 symptom screening

Temperature check and COVID-19 symptom (such as Stuffy or runny nose, Sore throat, Shortness of breath (difficulty breathing), Cough, Low energy or tiredness, Muscle or body aches, Headache, Chills or shivering, feeling hot or feverish (temperature check), vomiting, diarrhea, loss of sense of taste and smell) screening will be done for each subject at visit 1, 2, 3, 4 and Unscheduled / Early Discontinuation visit. During the screening, if the subject found to have any one of the above said symptoms, then it will be judged by the investigator whether it is related or not-related to COVID-19 and appropriate procedures will be followed by the investigator and site[10].

6.6 Lack of Treatment Effect (LOTE)

After completion of at least 4 weeks of the treatment period, if the subject comes to the Investigator and informs about not observing the desired treatment effect, then Investigator will evaluate the lesion counts and IGA scores and judge the lack of treatment effect. If the subject makes the decision to withdraw or discontinue from the study, then the reason for withdrawal/discontinuation will be coded as "lack of treatment effect (LOTE)." [redacted]

7 CLINICAL EVALUATIONS

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

[redacted]

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).

[redacted]

7.1 Investigator's Global Assessment (IGA)

At each study visit, beginning at Visit 1, an Investigator will assess the overall status of the Subject's face for acne vulgaris using the IGA. To be included in the study, subjects must have a definite clinical diagnosis of acne vulgaris of severity grade 2, 3, or 4 at screening/baseline.

The following scale will be used for the IGA:

Grade	Definition
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 will allow for reporting by Investigators of lesion worsening beyond Grade 4 with treatment. Subjects with nodulocystic acne vulgaris are not to be enrolled in the study. Subjects who worsen beyond Grade 4 will be described in the safety evaluation.

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

7.2 Lesion Counts

At each study visit, beginning at Visit 1, an Investigator will assess by counting the number of open and closed comedones (non-inflammatory lesions), pustules and papules (inflammatory lesions) and nodulo-cystic lesions from the jaw line to the hairline. All lesions will be counted,

[redacted]

including those present on the nose. Counts of nodules and cysts should be reported separately and not included in the inflammatory or non-inflammatory lesion counts. A papule with a pustule on its apex will be counted as a pustule. [redacted].

To be included in the study, subjects must have ≥ 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 screening/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

8 STUDY VISITS (SEE STUDY VISIT SCHEDULE)

8.1 Visit 1: Screening and 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 (up to the age of 40) must have provided IRB/IEC approved written informed consent. Subjects 12 to 17 years of age, inclusive, must have provided IRB/IEC approved written assent. Written assent must be accompanied by an IRB/IEC 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/informed assent form (IAF) 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. Both the ICF and assent (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. **Screening/Baseline Demographics: Demographics** will be collected, including date of birth, gender, race and ethnicity.
3. **COVID-19** symptom screening.
4. **Medical History**: 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)

5. **Vitals**: Vital signs (blood pressure, pulse, respiratory rate and body temperature) will be documented. Subjects must remain in a seated position for at least 5 minutes before vital signs are obtained.
6. **Physical Examination**: 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, Head, Eyes, Ears, Nose and Throat (HEENT), heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities.
7. **Concomitant Medications**: A complete list of current and past (within the previous 6-months) concomitant medications will be obtained for each Subject.
8. **Pregnancy Test:** A urine pregnancy test will be conducted for all females of childbearing potential.
9. **Clinical Assessment:** An evaluation of the patient's acne will be performed by an Investigator to determine the severity of the acne and confirm the diagnosis of acne vulgaris.
10. **Investigator Global Assessment**: The overall status of the Subject's facial acne vulgaris (from the jaw line to the hairline) will be assessed using the IGA.
11. **Lesion Count**: 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.

[redacted]

12. **Application Site Reaction**: Subjects will be evaluated for any signs and symptoms such as erythema, dryness, burning/stinging, erosion, edema, pain and itching.
13. **Inclusion/Exclusion Criteria**: 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.
14. **Adverse Events**: The occurrence of all AEs will be assessed and documented following procedures.
15. **Randomization:** Subjects will be randomly assigned in [redacted] to receive the Test product or the Reference Product or the Placebo control, respectively. [redacted]
16. **Investigational Medicinal Product and Supplies**: The following will be dispensed during Visit 1 post randomization by the Independent Dispenser:
    - The investigational product (1 pump)
    - [redacted]

Randomized Subjects will be instructed by the Independent Dispenser on the correct method for the application of the IMP. The application of the IMP will be performed by the Subject at home, instructed to apply the first dose in the evening. The study restrictions will also be reviewed with the Subject and an instruction sheet will be issued to the Subject.

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 time 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 IMP.

17. **Visit 2** (Day 28 [redacted] days from the date of Visit 1): will be scheduled and the Subject will be instructed to bring all IMP (used, unused, and partially used) and the Subject diary with him or her to this visit. Subjects will be reminded not to use any facial topical products within 12 hours prior to the next scheduled clinic visit.

[redacted]

8.2 Visit 2: First Interim (Week 4; Day 28 [redacted] Days)

The following procedures will be performed at Visit 2:

1. **Initial Check**: Temperature check and COVID-19 symptom screening.
2. **Pregnancy Test**: A urine pregnancy test will be conducted for all females of childbearing potential.
3. **Subject Compliance**: The Subject's compliance with the study protocol, including use, application and compliance of IMP, will be assessed. The Subject's diary will be collected and reviewed for completion.
4. **Investigational Medicinal Product**: The Subject's IMP dispensed at Visit 1 will be returned to the Independent Dispenser for review and re-dispensed if IMP remains.
5. **Concomitant Medication**: The use of concomitant medications since the previous study visit will be documented and assessed for each Subject.
6. **Adverse Events**: The occurrence of all AEs will be assessed and documented following procedures.
7. **Investigator Global Assessment**: The overall status of the Subject's facial acne vulgaris (from the jaw line to the hairline) will be assessed using the IGA by the Investigator or qualified staff member.
8. **Lesion Count:** 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.
9. **Application Site Reaction**: Subjects will be evaluated for any signs and symptoms such as erythema, dryness, burning/stinging, erosion, edema, pain and itching.
10. **Investigational Medicinal Product and Supplies:**

The following will be dispensed during Visit 2:

- The investigational product (1 pump) (new pump assigned through the randomization system and or pump from screening/baseline visit re-dispensed if sufficient IMP remains)
- [redacted]

[redacted] It is not anticipated that Subjects will require additional supplies during this visit; additional supplies will be dispensed if required.

[redacted]

11. Study instructions will be reviewed with the Subject, including the procedure for application of the IMP.
12. **Visit 3** (Day 56 [redacted] days from the date of Visit 1): will be scheduled and the Subject will be instructed to bring all IMP (used, unused, and partially used) and the Subject diary with him or her to this visit. Subjects will be reminded not to use any facial topical products within 12 hours prior to the next scheduled clinic visit.

8.3 Visit 3: Second Interim (Week 8; Day 56 [redacted] Days)

The following procedures will be performed at Visit 3:

1. **Initial Check**: Temperature check and COVID-19 symptom screening.
2. **Pregnancy Test:** A urine pregnancy test will be conducted for all females of childbearing potential.
3. **Subject Compliance**: The Subject's compliance with the study protocol, including use, application and compliance of IMP, will be assessed. The Subject's diary will be collected and reviewed for completion.
4. **Investigational Medicinal Product**: The Subject's IMP dispensed at the previous visit(s) will be returned to the Independent Dispenser for review, collection and or re-dispensed if IMP remains.
5. **Concomitant Medication**: The use of concomitant medications since the previous study visit will be documented and assessed for each Subject.
6. **Adverse Events**: The occurrence of all AEs will be assessed and documented following procedures.
7. **Investigator Global Assessment:** The overall status of the Subject's facial acne vulgaris (from the jaw line to the hairline) will be assessed using the IGA.
8. **Lesion Count**: 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.
9. **Application Site Reaction**: Subjects will be evaluated for any signs and symptoms of signs and symptoms of facial irritation such as erythema, dryness, burning/stinging, erosion, edema, pain and itching.
10. **Investigational Medicinal Product:**

The following will be dispensed during Visit 3:

- The investigational product (1 pump) (new pump assigned through the randomization system if required and or pump dispensed at Visit 2 re-dispensed if IMP still remains).
- [redacted]

[redacted]

- [redacted]

[redacted] It is not anticipated that Subjects will require additional supplies during this visit; additional supplies will be dispensed if required.

11. Study instructions will be reviewed with the Subject, including the procedure for application of the IMP.
12. **Visit 4** (Day 84 [redacted] days from the date of Visit 1): will be scheduled and the Subject will be instructed to bring all IMP (used, unused, and partially used) and the Subject diary with him or her to this visit. Subjects will be reminded not to use any facial topical products within 12 hours prior to the next scheduled clinic visit.

8.4 Visit 4: End of Treatment (Week 12; Day 84 [redacted] Days)

The following procedures will be performed at Visit 4:

1. **Initial Check**: Temperature check and COVID-19 symptom screening.
2. **Pregnancy Test:** A urine pregnancy test will be conducted for all females of childbearing potential.
3. **Subject Compliance**: The Subject's compliance with the study protocol, including use, application and compliance of IMP, will be assessed. The Subject's diary will be collected and reviewed for completion.
4. **Investigational Medicinal Product**: The Subject's IMP dispensed at the previous visit(s) will be returned to the Independent Dispenser.
5. **Concomitant Medication**: The use of concomitant medications since the previous study visit will be documented and assessed for each Subject.
6. **Adverse Events**: The occurrence of all AEs will be assessed and documented following procedures.
7. **Investigator Global Assessment:** The overall status of the Subject's facial acne vulgaris (from the jaw line to the hairline) will be assessed using the IGA.
8. **Lesion Count:** 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.
9. **Physical Examination**: 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, Head,

Eyes, Ears, Nose and Throat (HEENT), heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities.

10. **Application Site Reaction:** Subjects will be evaluated for any signs and symptoms of erythema, dryness, burning/stinging, erosion, edema, pain and itching.

8.5 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 the Early Discontinuation Visit 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 the reason for the unscheduled visit is documented and required procedures at the discretion of Investigator considering the reason for visit will be performed apart from the collection of IMP 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.

8.6 Premature Termination of Study/Study Site

The Sponsor reserves the right to discontinue the study at any time. The reasons will be discussed with the Investigator. A study site may also be discontinued by the Sponsor for significant deviations from the protocol or due to difficulties experienced in running the study at that center.

The Sponsor may terminate this study in one particular or several study center(s) for one (or other) of the following reasons:

a. Non-compliance with GCP and/or regulatory requirements

b. Centre cannot recruit an adequate number of subjects

c. False data captured in the eCRF due to carelessness or deliberately

d. Inadequate co-operation with the Sponsor or its representatives

e. The Investigator requests closure of his/her study center.

If the study is prematurely terminated in one or more study centers, all Investigators have to inform their subjects and take care of appropriate follow-up and further treatment of the subjects. Ethics Committees and regulatory authorities will be informed about the reason and time of termination according to the applicable laws and regulations.

The CRO should inform Teva Pharmacovigilance if the whole study is early discontinued due to safety reasons and should provide Teva Pharmacovigilance with the Early Termination Report.

8.7 Early Termination of a Subject

A subject may terminate from the study early for any reason at any time without any disadvantages. In this case, the Investigator should make every effort to have the subject return to the next scheduled visit to perform all required Early Termination (Early Discontinuation) visit activities and to collect and reconcile all study IMP. If the subject does not return for the Early Termination (Early Discontinuation) visit, the site should fully document the reason for early termination. All data, including the date and primary reason for termination, must be recorded on the Early Termination (Early Discontinuation) case report form (CRF), and source document.

Any subject who experiences an adverse event may be terminated from the study or from study treatment at any time at the discretion of the Investigator. In this case, the subject should be followed at the discretion of the Investigator until the resolution or stabilization of the AE. All applicable data should be recorded in the adverse events section of the case report form (CRF). If a subject terminates from the study early for multiple reasons that include adverse events, the Early Termination (Early Discontinuation) case report form should indicate that early termination was related to an adverse event.

An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant early termination but that requires the use of a prohibited medication, thereby requiring discontinuation of the subject. In such a case, the reason for discontinuation would be needed to take a prohibited medication, not the adverse event.

The Investigator must inform the Medical Monitor and CRO as soon as possible of all subjects who are being considered for early termination due to adverse events. Additional reports must be provided when requested. The CRO will inform the Sponsor of this event.

9 STUDY TREATMENT, DESCRIPTION AND ALLOCATION

9.1 Investigational Medicinal Products (IMP) Description

All study medications will be dispensed by and returned to a qualified Independent Dispenser designated by the Principal Investigator. The Independent Dispenser will not be involved in performing any of the clinical assessments (IGA, lesion count, evaluation of signs and symptoms of local irritation, or evaluation of safety).

The IMP will be dispensed only from the institution(s) approved by an Institutional Review Board.

The following treatments will be self-administered or administered by the Subject's caregiver during this study.

The IMP supplied in 45 gm pumps, by the Sponsor will consist of the following:

[redacted]

Test Product:	TRIFAROTENE CREAM, 0.005% (Manufactured by Actavis Laboratories, Salt Lake City, UT for Teva Pharmaceuticals, Inc.)
Reference Product:	AKLIEF® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA)
Placebo Control:	Placebo (Vehicle) topical cream (Manufactured by Actavis Laboratories, Salt Lake City, UT for Teva Pharmaceuticals, Inc.)

9.2 Storage and Handling Conditions

- Store at 20 to 25˚C (68 to 77˚F) with excursions permitted to 15°to 30°C (59° to 86°F) in a secured, authorized access area at the investigative site.
- Keep away from heat.
- Keep out of reach of children.

9.2.1 Packaging, Blinding and Labeling

[redacted] The labeling and packaging scheme will be outlined in a separate document by the Sponsor. The label content of IMP products will meet the requirements of ICH GCP guidelines, country specific guidelines and study protocol.

[redacted]. The study product will be packaged identically; an individual pump of study product (i.e., either Test, Reference or Placebo) will be packaged, as a "subject kit". Each subject will be assigned to one kit.

[redacted] all subjects consented and screened into the study will be assigned a "Subject Number." The Subject Number is the only subject identifier for subjects who are screened into the study (i.e., after being consented). The Subject Number is assigned, when a subject is screened into the study (i.e., after being consented). The study subject numbers will be assigned to study subjects sequentially in the order in which study subjects are enrolled into the study. [redacted]

[redacted]

Both the subject number and randomization number will be entered into the subject's eCRF. Each time a subject is dispensed study product (i.e., at Visit 1, and 2 or 3 as required, and when applicable unscheduled visit), [redacted]. Each subject will maintain the same subject number and treatment assignment throughout the study.

A label will be attached to each of the pumps of study product. The label will include at least the following information: Protocol number, subject number, study product kit number, space for subject's initials, statement that the study product is for Investigational Use only, space for dispensing date and the Sponsor's name. In addition, all subjects will be provided with written instructions on how to use the study product. .

[redacted] The study medications will be shipped to the Investigator's site from a centralized location.

This is a double-blind clinical endpoint bioequivalence study. The IMP will be labeled and packaged such that neither the Subject nor any Investigator or study can identify the treatment. The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the treatment assigned to the subject. [redacted]. The subject will be requested not to discuss the appearance of the study medication with the Investigator or study staff [redacted]

The Principal Investigator will be responsible for ensuring that all study products are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study medication will be maintained in accordance with federal regulations.

To ensure that information that could potentially bias handling of data is not disclosed, the packaging team will hold the randomization scheme until after database lock. At the end of the study, after all the clinical data has been entered and the study database has been locked, a copy of the randomization schedule will be sent to the statistician [redacted].

9.2.2 Randomization

The randomization schedule for this study will be generated [redacted] A copy of the randomization scheme (respective to that site) will be retained at the study site following the completion of the study and should be available to

regulatory authority inspectors at the time of site inspection to allow for verification of the treatment identity of each subject.

9.2.3 Subject Screening Number

Once a subject has signed the ICF, the subject will be assigned with a screening number, starting with three-digit site numbers followed by three-digit number starting from 001 in chronological order of screening in each site (e.g., 01001 for the first subject who signed ICF and screened at site 01). [redacted]

9.3 Treatment Assignment

The subject study identification number will correspond to a computer-generated randomization schedule assigning that number to one of the three study treatment groups. [redacted] The subject numbers at the site will correspond to the order in which subjects are enrolled into the study.

9.4 Administration of Investigational Medicinal Product

At Visit 1, IMP will be dispensed by the Independent Dispenser to randomized Subjects along with a diary. Each Subject will also receive written study instructions, which detail the proper application method of the IMP and general study instructions. Before each application, Subject should wash their face with a non-medicated cleanser (provided by the Sponsor), and pat dry. Skin should be allowed to dry for 20-30 minutes before applying study medication. The skin should be completely dry in order to minimize possible irritation. The Independent Dispenser will instruct the Subject not to open the IMP containers at the study center and to apply enough product to lightly cover the entire affected areas of the face once daily in the evening, preferably at bedtime.

Contact with the eyes, lips/mouth, angles/corners of the nose, open wounds and other mucous membranes should be avoided. Hands should be washed before and after applying the study medication. IMP should be applied in this manner daily for 84 days.

Subjects will be required to use diaries to document the date and time of application of study treatments, any missed treatments and the occurrence of all adverse events.

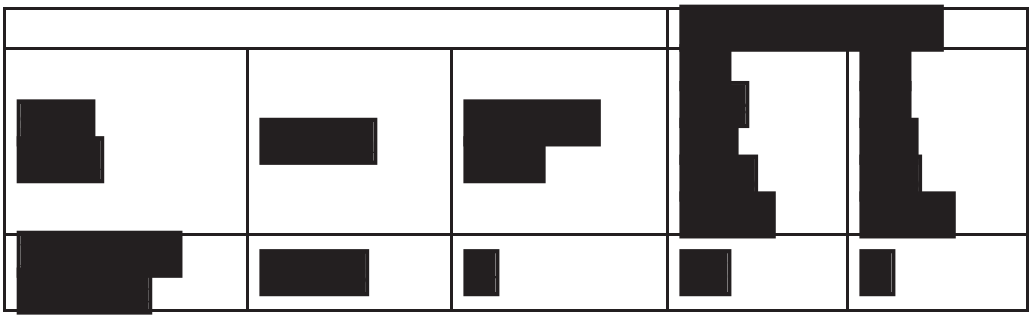
Subjects will be instructed not to bathe, shower, wash or swim for at least 4 hours after the application of the IMP.

9.5 Assessment of Compliance

Compliance with scheduled application of IMP will be determined from the Subject's diary. The

[redacted]

Subject will be instructed to use the diary to document all doses taken by checking the yes or no box for the appropriate date. In addition, Subjects will be instructed to document all concomitant medication and AEs on the diary. Used IMP will be returned to the study site at each scheduled visit or Early Discontinuation Visit or as applicable. If the subject does not return the Diary, compliance cannot be determined. [redacted]



9.6 Investigational Medicinal Product Accountability

It is the responsibility of the Principal Investigator to ensure that the current disposition of the IMP is maintained at each study site where IMP is inventoried and dispensed. When a drug shipment is received at a study site, the Principal Investigator or the Principal Investigator's Designee (for the purposes of this study the Independent Dispenser) must inventory the drug and sign the receipt form provided with the shipment. The receipt form should be emailed as per instructions provided on the receipt. A copy of the receipt should remain at the site.

The Principal Investigator at each site is responsible for ensuring that all investigational products are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). The Investigator will not supply study test articles to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

A **Drug Accountability Log** will assist study site staff in maintaining inventory records of study drug and is necessary for monitoring. An accurate inventory of the IMP will be maintained by the Independent Dispenser, in accordance with federal regulations. Subject's must return used, partially used or unused IMP to the Independent Dispenser, at the end of the study, (Visit 4) so that any remaining drug supplies can be accounted for and noted in the Drug Accountability Log.

The certified copy of Drug Accountability Log must be provided to the study monitor at the conclusion of the study and the original should remain at the study site.

[redacted]

Once the site has been notified that they may do so, all unused investigational product and empty or partially used pumps of investigational product, other than the randomly selected for retention samples, will be returned to the Drug Labeling, Packaging and Shipping Facility (Actavis Laboratories UT, Inc.) or be destroyed at the site after study close-out following approval from the Sponsor, and final drug accountability is reconciled.

9.7 Retention of Study Drug Samples

Enough of the study drug will be retained amongst the sites participating in the study to meet the sample retention requirements of the US-FDA 21 CFR 320.38, 320.63, Guidance for Industry "Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c)" and the Guidance for Industry "Handling and Retention of BA and BE Testing Samples".

Samples of study drug will be randomly selected at the investigational site, in accordance with 21 CFR 320.38, 320.63, Guidance for Industry "Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c)" and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding retention of study drug samples. and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the Investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP).

Each reserve sample will be stored under conditions consistent with product labeling [Store at room temperature between 20°C - 25°C (68°F to 77°F)] and with access limited to authorized personnel. Each reserve sample will be retained for a period **of at least 5 years** following the date on which the application or supplemental application is approved, or, if application is not approved, at least 5 years following the date of completion of the study.

[redacted]

The number of subject kits kept for retention will be noted on the study product accountability form, as a retention sample, in addition to the retention sample log. The study site PI is responsible for storage of retention samples while at the site, until shipment to a third-party repository.

To ensure samples are not confused with investigational product for subject use and to ease the storage burden at a site, the randomly selected retention samples of investigational product will be transferred by the sites to an independent biorepository vendor, an independent third-party storage facility for long term storage. To ensure compliance with product specific storage requirements, the original label should not be covered with a new shipping label. [redacted]

[redacted]

[redacted]

The samples can be retrieved from the storage facility at any time upon FDA notification of the visit or during a pre-approval inspection conducted by authorized FDA personnel. The samples can be returned to the investigational site or submitted to the place identified in the agency's request. The request has to be sent directly to an independent biorepository vendor by email or fax from the site. The Sponsor (Teva Pharmaceuticals, Inc.) [redacted] must be notified, and copies of documentation should be sent to the individuals listed below:

Retention Samples Storage Facility	Sponsor	Clinical Research Organization:
[redacted]	[redacted]	[redacted]

9.8 Return of Clinical Supplies

Except for the retention samples, all used and unused pumps of IMP may be returned to the Drug Labeling, Packaging and Shipping Facility (Actavis Laboratories UT, Inc.) for destruction or be destroyed at the site after study close-out following approval from the Sponsor, and final drug accountability is reconciled.

It is important that retention samples and all used and unused pumps of IMP not be returned to [redacted] or the Sponsor (Teva) at the end of the study.

9.9 Additional Supplies Provided by The Sponsor

[redacted]

[redacted]

[redacted]

10 STATISTICAL METHODS

10.1 Scientific and Statistical Considerations of the Study Design

The study was designed following FDA Draft Guidance on Trifarotene Recommended May 2021[6] and FDA Draft Guidance on Adapalene; Benzoyl peroxide Gel; topical, Recommended Dec 2016; Revised Nov 2018, Nov 2019[7] and Guidance for Industry -Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment, May 2018[4].

10.1.1 Sample Size Rationale

Sample size calculations are based on information from a Medical Review[11] for developing a bioequivalence study comparing Trifarotene cream 0.005% after 12 weeks of treatment. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.1.2 Unblinding Procedures

This is a Randomized, Double-blind, Three-Arm, Placebo Controlled, Parallel design, multi-centre study. Subjects will be randomly assigned [redacted] to receive the test product, the reference product and the vehicle (placebo) control. The randomization assignment will be generated using SAS® by [redacted] The treatment each subject will receive will not be disclosed to the Investigators, study center personnel, subject, sponsor, or CRO involved in the study conduct, monitoring, data review or analysis.

[redacted] If necessary, for the safety and proper treatment of the subjects, the Investigator can unblind the subject's treatment assignment to conduct appropriate follow-up care. Whenever possible, the Sponsor or medical monitor will be notified before unblinding the study medication. The date and signature of the person breaking the code as well as the reason for breaking the code and any associated AEs will be recorded in the subject's source documentation.

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the treatment assigned to the subject, with the exception of the Independent Dispenser. The study site will have at least one Independent Dispenser. The role of the unblinded Independent Dispenser will be to dispense and collect study medication to/from the subjects, maintain dispensing records, and ensure the study medication logs are complete and accurate. The subject will be requested not to discuss the appearance of the study medication with the Investigator or study staff outside of the Independent Dispenser. Independent dispenser should not participate in any activities other than the activities defined in this section.

In case of an emergency, if the details of the study drug are required for management of an emergency as per the opinion of Investigator, the Investigator can unblind the product that is received by the subject during the study. In case of non-emergency condition that requires study drug information for management of condition as per Investigator's opinion, the Investigator should obtain Sponsor or medical monitor approval in writing prior to breaking of the blind. [redacted] It is recommended that all attempts should be made to maintain the study blind. However, in case that unblinding is performed, the reason for breaking the blind must be clearly documented in the source documentation and Case Report Form (CRF) and the subject must be discontinued from the study.

The date on which the code was broken together with the identity of the person responsible must also be documented.

The treatment assignments will remain blinded until the final database is locked.

[redacted]

10.1.3 Significance Level

All statistical tests will be two-sided at a significance level of $\alpha = 0.05$, unless otherwise indicated. No adjustment will be made for multiplicity.

10.2 Datasets to be Analyzed

Three analysis populations will be used in the analysis of the clinical data:

[redacted] proper administration of the treatment or accurate evaluation of its effectiveness.

[redacted]. In addition, subjects whose condition or symptoms worsens and require alternate or supplemental or rescue therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population analysis using LOCF, and provided with effective treatment. The use of supplemental medicines and rescue medicine will be per standard of care (SOC) per medical judgement of the Investigator. All supplemental and rescue medicines will include name, dose, frequency of administration, start and end dates, which is supplied to discontinued subjects for worsening of conditions.

[redacted] If subject makes the decision to withdraw or discontinue from the study, then the reason for withdrawal/discontinuation will be coded as "lack of treatment effect" (LOTE). [redacted]

A shift table will be provided for any subject that has been discontinued with the reason of lack

of treatment effect to show changes from screening/baseline to time of discontinuation (last observation).

10.3 Measures

At each visit, beginning at Visit 1, an Investigator will assess the overall status of the Subject's facial acne vulgaris using the Investigator's Global Assessment (IGA) and the Lesion Counts.

Local irritation/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.

10.3.1 Demographics and Screening/Baseline/Randomization Characteristics

Demographic and screening/baseline/randomization characteristics will be evaluated for comparability across treatment groups for the mITT, PP, and safety populations. Continuous variables will be analyzed with an analysis of variance with factors of treatment and investigational site. Categorical variables such as gender, ethnicity, and race will be analyzed with a Cochran-Mantel-Haenszel test, stratified by investigational site.

10.3.2 Safety Assessment

The extent of exposure will be summarized using descriptive statistics. No inferential analyses are planned.

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 comparability of the Test and Reference treatment groups for the frequency and severity of any adverse event that occurs in at least 5% of the subjects in either treatment group will be evaluated using categorical methods.

The concomitant medications used will be summarized by treatment group.

Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching will be summarized for the safety population by treatment group and study visit using frequencies and percentages of subjects.

Safety analyses will be performed on the safety population. All safety data will be listed by treatment and Subject in data listings.

10.3.3 Efficacy Assessment

10.3.3.1 Primary Endpoints

The primary efficacy endpoints are the mean percent change from screening/baseline to week 12 in the inflammatory (papules and pustules) and in the non-inflammatory (open and closed comedones) lesion counts.

10.3.3.2 Test of Clinical Equivalence

The evaluations of clinical equivalence will be performed for the PP population.

For the primary efficacy assessment, the two-sided, 90% confidence interval on the test/reference ratio of the mean percent change from screening/baseline to week 12 in each lesion type will be calculated using Fieller's method and the pooled variance estimate (MSE) obtained from a two-way Analysis of Variance (ANOVA) of the Test and Reference results. The statistical model for the ANOVA will contain terms for treatment and center. If the skewness of the residuals from the ANOVA is outside of -2 to 2, then a nonparametric approach will be used to obtain the confidence intervals. Bioequivalence will be established if the 90% confidence intervals for the ratio of test/reference means, for both inflammatory and non-inflammatory lesion counts, are contained within the interval [0.80, 1.25] using the per protocol (PP) population.

10.3.3.3 Test of Superiority

The evaluations of superiority will be performed using the mITT population.

Superiority of the Test treatment versus the Vehicle and for the Reference treatment versus the Vehicle will be conducted separately.

The test product and RLD will each be compared to that of the placebo group separately using ANOVA to evaluate if they are statistically superior at $p<0.05$ (two-sided test) to the placebo. Superiority will be established If the mean percent change (reduction) from screening/baseline to week 12 for each active treatment, for both inflammatory and non-inflammatory lesion counts, is greater than, and statistically different from ($p<0.05$), that for the vehicle (placebo) Control.The statistical model for the ANOVA will contain terms for treatment and center. If the skewness of the residuals from the ANOVA is outside of -2 to 2, then a nonparametric approach will be used.

10.3.3.4 Analysis of IGA scores

Descriptive statistics using categorical methods to compare IGA Scores between each treatment group will be conducted and presented. No inferential analyses are planned.

10.3.3.5 Analysis of Application Site Reactions

Descriptive statistics using categorical methods to compare application site reactions between each treatment group will be conducted.

10.4 Concomitant Medication

The start and stop calendar date (e.g., dd/mmm/yyyy) and study day (e.g., Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. It should clearly be noted whether the medication was used prior to screening/baseline visit, during the study, or both.

10.5 Summary of Subjects who discontinued prematurely

Reasons for early discontinuation will be summarized by treatment group.

11 ADVERSE EVENTS

11.1 Recording of Adverse Events

An adverse event is any untoward medical occurrence in a Subject administered a medicinal product regardless of whether it has a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the medicinal product. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

1. intercurrent illnesses
2. physical injuries
3. events possibly related to concomitant medication
4. significant worsening (change in nature, severity, or frequency) of the disease under study or other preexisting conditions
5. events occurring during diagnostic procedures or during any washout phase of this study
6. laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, or require medical treatment or further diagnostic work up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events).
7. side effects caused by drug interaction.

The potential adverse reactions of TRIFAROTENE CREAM, 0.005% (Teva Pharmaceuticals, Inc.) are anticipated to be similar to those observed with the use of AKLIEF® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA). The skin of certain sensitive individuals may become excessively red, edematous, swollen, blistered or crusted, local erythema, peeling at the site of application. Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin. **Trifarotene, like other retinoids, has been reported to cause severe irritation on eczematous skin and should be used with utmost**

caution in patients with this condition.

Worsening of the disease under study will be measured by an increase in the IGA score by one or more grades, and should be recorded as an adverse event only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular subject.

In this study, any adverse event occurring after the subject has signed the informed consent/assent form until the end of follow-up period should be recorded and reported as an adverse event.

A treatment-emergent AE (TEAE) is any AE that occurs after initiation of study medication, or any event already present that worsens in either intensity or frequency following exposure to study medication.

For adverse event recording, the study period is defined for each subject as that time period from signature of the informed consent/assent form through the end of the study (including the follow up period). All adverse events that occur during the defined study period must be recorded on the source documentation and CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the Serious Adverse Event Form must also be completed, and the serious adverse event must be reported immediately (see Section on Reporting below).

At each contact with the subject, the Investigator or designee must question the subject about adverse events by asking an open-ended question such as, “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings may be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, also on the Serious Adverse Event Form.

The onset and end dates and times, action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation.

The relationship of each adverse event to study drug treatment, and the severity and seriousness of each adverse event, as judged by the Investigator, must be recorded as described below.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to screening/baseline, until the subject is referred for continued care to a health care professional or until a determination of a cause unrelated to the study drug or study procedure[1] is made.

Adverse events will be coded according to MedDRA (Medical Dictionary for Regulatory Activities) and reported with respect to severity, duration, relationship to study medication(s), seriousness, outcome and action taken.

11.1.1 Assessment of Severity

The severity of each adverse event must be recorded as 1 of the choices on the following scales:

- Mild: No limitation of usual activities
- Moderate: Some limitation of usual activities
- Severe: Inability to carry out usual activities

11.1.2 Relationship to Study Medication

Adverse events will be assessed for the relationship to the study drug (causality) according to the following scale:

TERM	DEFINITION	CLARIFICATION
No Reasonable Possibility (not related)	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those adverse events, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	• An adverse experience may be considered • No Reasonable Possibility if it is clearly due to extraneous causes or when (must have two): • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.

Reasonable Possibility (related)	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty or felt with a high degree of certainty to be related to the test drug.	• An adverse experience may be considered Reasonable Possibility related if or when (at least two of the following): • It follows a reasonable temporal sequence from administration of the drug. • It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. • It follows a known pattern of response to the test drug.

11.2 Serious Adverse Events

An **Adverse Event or Suspected Adverse Reaction** is considered ''serious'' if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- A life-threatening adverse event; (Note: the term "life-threatening" as used here refers to an event in which the Subject was 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 was more severe.)
- Requires in-Subject hospitalization or prolongation of existing hospitalization; This means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an AE, or that they occurred as a consequence of the event. Hospitalizations scheduled prior to study entry will not be considered SAEs, unless there was worsening of the pre-existing condition during the subject's participation in this study.
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions).

- Is a congenital anomaly/birth defect.
- Any "other" important medical event.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered Serious Adverse Events when, based on appropriate medical judgment, they may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious adverse event.

Regardless of the above, any additional adverse events, which the Principal Investigator considers significant, should be immediately reported to the CRO [redacted]

11.2.1 Expectedness

The sponsor's Pharmacovigilance Department will determine the expectedness for all serious adverse events. CRO and Investigators will not determine the expectedness.

An AE which is not included in the adverse events section of the relevant Safety Information Reference by its specificity, severity, outcome or frequency is considered an unexpected adverse event.

The reference safety information for this study is AKLIEF® (TRIFAROTENE 0.005% CREAM) (GALDERMA LABORATORIES, L.P., USA, Prescribing Information to use as reference for safety information is to be found in Appendix II.

11.3 Reporting of Serious Adverse Events (SAEs)

To satisfy regulatory requirements, all serious adverse events (as described in Section 11.3) that occur during the study period (including the protocol defined follow up period) regardless of judged relationship to treatment with the study drug, must be reported to [redacted]

[redacted]

PLEASE NOTE THAT EMAIL IS THE PREFERRED MEANS OF COMMUNICATION.

All SAEs must be reported in parallel to the following persons:

1. Appropriate Pharmacovigilance (PhV) unit:

[redacted]

The SAE form should be completed, preferably in English. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact. Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded within 24 hours of the information becoming available to the same address as the initial report.

[redacted]

The reporting timelines for reporting of SAE's by the Investigator to the CRO and LSO (if applicable) (depending on the type of study) is within 24 hours. If the Investigator exceeds 24 hours to report the SAE, this should be identified as a protocol deviation and documented accordingly.

In case, the Investigator fails to report any serious adverse event within the stipulated period, he/she shall have to furnish the reason for the delay to the satisfaction of the IRB along with the report of the serious adverse event. The report of the serious adverse event, after due analysis, shall be forwarded by the Investigator to IRB, Sponsor (Teva) and CRO within fourteen days of the occurrence of the serious adverse event as referred in clause (ix)-section 35 of Part-B of Chapter-V of New Drugs & Clinical Trial Rules; 2019. The study site must transmit the SAE form through an email to and Teva contacts listed above.

These SAE reports must contain the following information, preferably using the template provided by the Sponsor:

A. Study name/number

B. Study Drug

C. Investigator details (name, phone, fax, e-mail)

D. Subject Number

E. Subject Initials when appropriate

F. Subject Demographics

G. Clinical Event

1) Description

2) Date of onset

3) Treatment (drug, dose, dosage form)

4) AE Relationship to study drug

5) Action taken regarding study drug in direct relationship to the AE

H. If the AE was Fatal:

1) Cause of death (whether or not the death was related to study drug)

2) Autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the Investigator and the sponsor pharmacovigilance to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

For studies conducted in USA: It is the responsibility of the CRO to report a Serious Adverse Event (SAE) to the FDA within proper time constraints as per the Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies – please refer to the most current version. Confirmation of submission of this report must then be provided to Teva's study representative as well as their Pharmacovigilance department (contact info below).

The timeliness for submission of expedite reports should be 15 days or 7 days (death cases) or as otherwise specified in local regulations.

The CRO will take on the responsibility of reporting SAEs to the Investigators and/or to the Ethic Committee.

Any serious adverse event will be reported to competent authority and ethics committee according to the country specific requirements and the responsibilities defined above. All AEs will be reported in the Clinical Study Report with the complete information named above according to the requirements of the Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).

Subjects who have had an SAE during the study must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained. The Investigator does not need to actively monitor subjects for new serious adverse events once the study has ended. However, serious adverse events occurring after a subject ended the study should be reported to the Sponsor if the Investigator becomes aware of them.

11.4 Pregnancy

Female subjects of childbearing potential must have been using and must agree to continue to use accepted methods of birth control, throughout the study and demonstrate negative pregnancy tests.

All female subjects are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized (by *hysterectomy or bilateral oophorectomy) or have been postmenopausal for at least 1 year. Tubal ligation is not considered equivalent to female sterilization. Women with a history of tubal ligation are still considered females able to become pregnant and must complete a urine pregnancy test.

Alternatively, any of the following methods of birth control are acceptable: oral or injectable contraceptives, contraceptive patches, medroxyprogesterone acetate (ex. Depo-Provera®) with stabilized use for at least 3 months), vaginal contraceptive (etonogestrel/ethinyl estradiol vaginal ring (ex. NuvaRing®)) contraceptive implant with etonogestrel or equivalent, double barrier methods (e.g., condom and spermicide), IUD, abstinence.

If a subject who was abstinent becomes sexually active during the study, a 2nd acceptable method of birth control should be used and documented. Prior to study enrollment women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation.

*Full hysterectomy or bilateral oophorectomy considered surgically sterile. Tubal ligation is not considered equivalent to female sterilization.

A negative result of a pregnancy test having a minimum sensitivity of at least 25 mIU/ml for hCG should be obtained, prior to study procedures, at Visit 1.

Pregnancy testing will also be performed at every study visit and the results of all pregnancy tests (positive or negative) will be documented. Subjects must have a negative urine pregnancy to continue in the study.

All pregnancies of women participating in the study that occur during the study, or within at least 5 half-lives, or 30 days for unknown half-lives days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the Investigator must provide the Sponsor with the completed pregnancy form. The process for reporting a pregnancy to the Sponsor is the same as that for reporting a serious adverse event but using the pregnancy form as provided by the Sponsor.

Any female subject/patient becoming pregnant during the screening period (i.e., before study drug administration) will be considered a screen failure and will not be allowed to rescreen. The Investigator is not required to report such pregnancies, provided no protocol-related procedures with known risk on pregnancy were applied.

Any female subject becoming pregnant during the study will discontinue treatment. All subjects who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the Sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the Investigator becomes aware of after termination from the study will be reported as an adverse event or serious adverse event, as appropriate.

11.5 Follow Up of Subjects

The staff of the clinical facility/site has to monitor the clinical trial subject's safety from the occurrence of an AE until satisfactory recovery.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to screening/baseline, until the subject is referred for continued care to a health care professional or until a determination of a cause unrelated to the study drug or study procedure is made.

Any AE which remains unresolved at the time point of subject’s last visit requires detailed evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence is found; in case of AEs related to the IMPs every effort has to be made to follow-up clinical trial subjects to determine the final outcome. If follow-up cannot be completed until release of CRF by the investigator the individual CRF will be released and transferred to the Clinical Data Management. In this case, follow-up information will be documented separately in the subjects’ record and outcome including a short description on follow-up procedures performed must be sent to the sponsor.

It is the Investigator’s responsibility to assure that subjects experiencing adverse reactions will

receive definitive treatment for any adverse reaction, if required. Details of follow-up care are to be provided (i.e., if treatment or hospitalization is required). The responsibility to provide adequate follow-up for AEs includes periodically repeating laboratory tests yielding clinically abnormal results at the end of study evaluation.

11.6 Medication Errors and Special Situations

Any administration of study drug that is not in accordance with the study protocol should be reported in the subject's source documents (and in the eCRF), regardless of whether or not an adverse event occurs as a result.

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
3. Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information or the study protocol.
4. Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
5. Occupational exposure: Exposure to a medicinal product, as a result of one’s professional or non-professional occupation.
6. Lack of efficacy.

11.7 Reconciliation of SAEs & Pregnancy

It is the CRO responsibility throughout the course of the study, to maintain a listing of all SAEs and pregnancy reports. At the conclusion of the study, in the case that NO SAE/pregnancy occurred, the CRO should send an email to Teva Global PV to indicate that no SAE/pregnancy occurred during the study. In the case that a SAE/pregnancy did occur, the CRO should send an email to PV requesting the reconciliation line listing. The CRO should perform a reconciliation of the SAEs in the study with those in the Teva Global PV database.

All communication regarding Safety Data Reconciliation should be directed to [redacted]

11.8 Safety Considerations during COVID-19 Pandemic

The safety of site staff and study subjects are to be protected against possible transmission of COVID-19. All sites should develop a detailed plan or SOP on how to mitigate risks of exposure

to the virus as well as protect participants and study staff while maintaining study integrity. SOPs/site specific plan should include methods to reduce the amount of time spent by the study participant at study site and any interactions with site staff and study subjects.

At each visit, temperature check and COVID-19 symptom (such as tuffy or runny nose, sore throat, shortness of breath (difficulty breathing), cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, vomiting, diarrhea, loss of sense of taste and smell) screening for study subjects and site staff will be performed. At each visit, site should also ensure, subject exposure to others with suspected or confirmed SARS-CoV-2 infection.

Study subjects and site staff should wear appropriate personal protective equipment/masks and practice hand sanitization methods. Site should ensure physical distancing (maintaining at least 6 feet between people) and take appropriate action to prevent possible infection from the COVID viruses as an important strategy where possible. Sites should assign only one participant per room, while performing any general safety evaluations or assessments and should disinfect the room once the participant leaves.

Care should be taken to ensure study integrity and scientific validity of the data generated due to modifications to study conduct or design. Subject that has tested positive for COVID-19 during the trial may be discontinued from the study as per investigator's discretion.

12 ETHICS

12.1 IRB/Ethics Committee

IRB/Ethic committee (IRB/EC) approval will be obtained from an EC registered with FDA. PI will provide the Sponsor or [redacted] with documentation of IRB/EC approval of the protocol, ICF, advertising material and all documents required as per applicable regulations before the study may begin at the study sites. Site shall maintain all the study records for no less than 5 years from the date of study completion or termination of the trial. PI will supply documentation for IRB/EC's annual renewal to the Sponsor or [redacted] and provide any IRB/EC approvals of revisions to the informed consent or protocol amendments.

The PI will report promptly to the IRB/EC, any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the PI will submit written summaries of the study status to the IRB/EC annually, or more frequently if requested by the IRB/EC. Upon completion of the study, the PI will provide the IRB/EC with a brief report of the outcome of the study, if required.

12.2 Ethical Conduct of the Study

This study will be conducted, and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (2013), FDA regulations, the applicable guidelines for GCP and/ or the applicable local drug and data protection laws and regulations.

The study will be conducted in compliance with the protocol.

The rights, safety and well-being of the study subjects are the most important considerations and should prevail over interests of society and science.

12.3 Informed Consent/Assent

The Principal Investigator must ensure that subjects and/or their legally acceptable representative (i.e., parent or guardian) are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. The principles of Informed Consent/Assent, according to FDA Regulations and ICH GCP will be followed. A copy of the proposed consent/assent form must be submitted to the IRB/IEC, together with the protocol, for approval. Prior to beginning of the study, the Principal Investigator must have the IRB/IEC's written approval of the written informed consent/assent form and any other information to be provided to Subjects.

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant [or their legally authorized representative and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They [or their legally authorized representatives] will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant [or their legally authorized representative].

Informed consent/assent will be obtained from all subjects using the following procedure: Subjects who are 18 years of age or older (up to the age of 40) must have provided IRB/IEC approved written informed consent. Subjects 12 to 17 years of age, inclusive, must have provided IRB/IEC approved written assent. Written assent must be accompanied by an IRB/IEC 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. Both the ICF and

assent (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.

12.4 Subject Confidentiality

The monitor(s), the auditor(s), IRB/IEC, and the regulatory authority(ies), will be granted direct access to the Subject's original medical records for verification of the clinical trial procedures and/or data, without violating the confidentiality, to the extent permitted by the applicable laws and regulations and that by signing a written informed consent form, the Subject or the Subject's legally acceptable representative is authorizing such access.

The identity of the Subject will not be made publicly available and will be kept confidential and, to the extent permitted by the applicable laws and regulations and meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPPA privacy and data protection requirement. If the results of the trial are published, the Subject's identity will remain confidential.

13 DOCUMENTATION

13.1 Site Regulatory Documents Required for Initiation

At a minimum, the following documents will be received by the CRO prior to the initiation of the study:

1. Completed and signed FDA Form 1572
2. Current curricula vitae, signed and dated for the Principal Investigator and each Sub-Investigators named in the FDA form 1572 (current within 2 years)
3. Current medical licenses of the Principal Investigator and each Sub-Investigator named in FDA form 1572
4. Documentation of IRB/IEC approval of this study protocol, Principal Investigator and informed consent/assent forms
5. Current IRB/IEC membership list or roster
6. Fully executed protocol, and a copy of the protocol agreement page and any applicable amendments signed by the Principal Investigator
7. Documentation of "No Objection" to proceed from the local regulatory agency, wherever applicable.
8. Non-disclosure Agreements for the investigator site named in FDA form 1572
9. Financial Disclosure Statement for the Principal Investigator and each Sub-Investigator named in FDA form 1572.
10. Statement of Non-Debarment

13.2 Maintenance and Retention of Records

It is the responsibility of the Principal Investigator to maintain a comprehensive and centralized

filing system of all relevant documentation[8, 9].

Copies of all pertinent records will be retained by the Principal Investigator for at least two years following final approval of the drug and/or notification from the Sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities. These records include documents pertaining to the receipt and return of drug supplies, IRB/IEC, informed consent, source documents. No documents shall be transferred from the site or destroyed without first notifying the Sponsor. If the Principal Investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee in agreement with [redacted] and Sponsor. Notice of such transfer will be given in writing to the Sponsor.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories designed to document all observations and other data pertinent to the investigation on each individual treated with the IMP or entered as a control in the investigation. Data reported on the CRF, which are derived from source documents, must be consistent with the source documents.

13.3 Data Collection and Reporting

Data for individual subjects will be collected on eCRF. The data management system will be Electronic Data Capture (EDC). The Investigator and his/her study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded in the eCRFs. All information requested in the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

Source documents such as the clinic chart (medical records specifically collected for the study information) are to be maintained separately from the eCRF in order to allow data verification. Because of the potential for errors, inaccuracies and illegibility in transcribing data into eCRFs, originals of laboratory and other test results must be kept on file. Source documents and copies of test results must be available at all times for inspection by the study monitor or any applicable auditors. The following should also be available for review:

1. **Subject Screening Log** – documenting all subjects screened for participation in the study and reflecting their eligibility status. If ineligible, the reason the subject was ineligible should be documented
2. **Delegation of Authority / Study Personnel Signature Log** – all site personnel will be listed along with their responsibilities and signatures; to be maintained at the site throughout the study
3. **Monitoring Log** – the date and purpose of all monitoring visits by the CRO representative/Sponsor/Designee will be documented
4. **Enrollment Log** – documenting Subject initials and start and end dates for all subjects enrolled

5. **Drug Inventory/Packing Slip** – reflecting the total amount of drug shipped to the site and received and signed by the Principal Investigator
6. **Drug Accountability Log** – reflecting the total amount of IMP dispensed to and returned by each Subject
7. **Informed Consent Form and Assent Form** – which must be available for each Subject and be verified for proper documentation

The study monitor will be responsible for reviewing and verifying the data recorded in the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. All queries issued by the data management personnel will be answered by site personnel and verified by the monitor.

13.4 Primary Source Documents

The Principal Investigator must maintain primary source documents supporting significant data for each Subject's medical notes. These documents, which are considered "source data", should include documentation of:

1. Demographic information
2. Evidence supporting the diagnosis/condition for which the Subject is being studied
3. General information supporting the Subject's participation in the study
4. General history and physical findings
5. Hospitalization or Emergency Room records (if applicable)
6. Each study visits by date, including any evaluations, relevant findings/notes by the Principal Investigator(s), occurrence (or lack) of adverse events and changes in medication usage, including the date the study drug commenced and completed.
7. Any additional visits during the study
8. Any relevant telephone conversations with the Subject regarding the study or possible adverse events
9. An original, signed informed consent form/assent form (as applicable) for study participation
10. Subject Diary

The Principal Investigator must also retain all Subject specific printouts/reports of tests/procedures performed as a requirement of the study. During monitoring visits, the monitor will need to validate data in the eCRFs against these sources of data.

13.5 Study Monitoring

The study will be monitored by a representative of the CRO/sponsor (as applicable) to assess compliance with the protocol, ICH-GCP and applicable regulations. The Principal Investigator will be visited by a monitor prior to the study and at regular intervals during the course of the study. These visits are for the purposes of verifying adherence to the protocol.

The study monitor will review the Informed Consent/Assent Forms and verify eCRF entries by comparing them with the source documents (hospital/clinic/office records) that will be made available for this purpose. The monitor will review the maintenance of regulatory documentation and drug accountability. The monitor will review on a regular basis the progress of the study with the Principal Investigator and other site personnel.

eCRF sections may be monitored during these visits. At the end of the study, a closeout monitoring visit will be performed. Monitoring visits will be arranged in advance at a mutually acceptable time with site personnel. Sufficient time must be allowed by the site personnel for the monitoring of eCRFs and relevant source documents. The Study Coordinator and/or Principal Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the Principal Investigator.

13.6 Audits and Inspections

During the study and/or after it has been completed, one or more site visits may be undertaken by auditors as authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the protocol, recognized GCP guidelines and all applicable regulations.

Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during the study and/or after it has been completed.

THE INVESTIGATOR MUST NOTIFY THE CLINICAL RESEARCH ORGANIZATION AND/OR SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

13.7 Modifications to the Protocol

The procedures defined in the protocol will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no deviations from the protocol, with minimal exceptions, may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the Sponsor and the IRB/IEC prior to implementation.

The only circumstance in which an amendment may be initiated without prior IRB/IEC approval is to eliminate apparent immediate hazards to a Subject or Subjects. However, the Principal

Investigator must notify the Sponsor immediately and the IRB/IEC within 5 working days after implementation.

All protocol deviations will be reported on the Protocol Deviation Log and included in the study reports. A protocol deviation is defined as any change, deviation from the study design or procedures of research project that is NOT approved by the IRB/IEC prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations.

14 COMPLETION OF STUDY

The Principal Investigator is required to sign the eCRFs and forward all other relevant data and records to the CRO.

The Principal Investigator is expected to submit a final report to the IRB/IEC and the Sponsor within one (1) month of study completion or discontinuation. CRO must submit a final report as agreed in the Study Agreement for this study between Sponsor and CRO.

15 REFERENCES

1. Kurokawa I, Layton AM, Ogawa R. Updated Treatment for Acne: Targeted Therapy Based on Pathogenesis. Dermatol Ther (Heidelb). 2021 Aug;11(4):1129-1139
2. Baldwin H, Webster G, Stein Gold L, Callender V, Cook-Bolden FE, Guenin E. 50 Years of Topical Retinoids for Acne: Evolution of Treatment. Am J Clin Dermatol. 2021 May;22(3):315-327.
3. Bell KA, Brumfiel CM, Haidari W, Boger L. Trifarotene for the Treatment of Facial and Truncal Acne. Ann Pharmacother. 2021 Jan;55(1):111-116
4. FDA Guidance for Industry. Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment. Food and Drug Administration. May 2018.
5. FDA Label (DailyMed) for Trifarotene Revised: Oct 2019
6. FDA's Draft Guidance on Trifarotene (May 2021)
7. FDA's Draft Guidance on Adapalene; Benzoyl peroxide (gel, 0.3%; 2.5%), Recommended Dec 2016; Revised Nov 2018, Nov 2019.
8. Guidance for Industry. Handling and Retention of BA and BE Testing Samples. Office of Generic Drugs. FDA. May 2004.
9. Guidance for Industry "Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c)
10. FDA Guidance for Industry. Protecting Participants in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency. January 2021.

11. FDA Summary Basis of Approval. Alkief # 211527 October 2019

[redacted]

15.1 APPENDIX I: Revision History

Version #	Affected Sections
Final 1.0 (13May2022)	N/A (new)
Final 2.0	1. Section 9.2.1 Packaging, Blinding and Labeling: Revisions made to account for change in IMP pump label to not use 2-part scratch off label 2. Study Population - Inclusion Criteria #3 (Page 14): Removed the word “treatment” 3. Section 5.1.1 – Inclusion Criteria #3 (Page 29): Removed the word “treatment” 4. Section 9.2.3 – Subject Screening Number (Page 59) Revised Screening Number to include a three-digit Site Number, instead of a two-digit Site Number 5. Section 10.1.2 - Unblinding Procedures (Page 64): Removed scratching off the tear off blinding label on IMP as a way to perform unblinding In addition, administrative and editorial changes have been made throughout the version 2 protocol to improve readability and syntax

15.2 APPENDIX II: AKLIEF-trifarotene cream package insert

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Certificate Of Completion

Envelope Id: 0D9D795CDE6B46F79AE5D83DDB6190BA

Status: Completed

Subject: Please DocuSign: TRIF-2101_Protocol_Version 2.0_30Jun2022_FINAL_Med Monitor Signed_AS_Stats Sig...

Source Envelope:

Document Pages: 88

Signatures: 2

Envelope Originator:

Record Tracking

Status: Original

21-Jul-2022 | 12:29

Location: DocuSign

Signer Events

Events

Status

Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	21-Jul-2022 | 12:31
Certified Delivered	Security Checked	21-Jul-2022 | 12:51
Signing Complete	Security Checked	21-Jul-2022 | 12:55
Completed	Security Checked	21-Jul-2022 | 17:29

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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If you have any concerns about how we process your personal data or wish to exercise any of your rights or wish to obtain other information, such as a copy of a legitimate interests balancing test, you can get in touch with [redacted]

[redacted] We hope that we can satisfy any queries you may have about the way in which we process your personal data. However, if you have unresolved concerns you also have the right to complain to the data protection authority in the location in which you live, work or believe a data protection breach has occurred.

International Transfers

[redacted]

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Specifically, these electronic systems must comply with Title 21 of the Code of Federal Regulations (21CFR Part 11) relating to electronic records and electronic signatures. This affidavit is required for each employee using an electronic signature and must be signed prior to his/her use of electronic signatures.

Please read this affidavit and sign below to signify that you have read and understood this affidavit.

Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations, the undersigned hereby certifies that his/her electronic signature is the legally binding equivalent of his/her traditional handwritten signature.

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Updated: May 2021