# A Randomized, Evaluator-Blinded, Bilateral Comparison Study of Two Topicals in the Treatment of Subjects with Acne Vulgaris

**ClinicalTrials.gov Identifier: NCT03743038**

**Date of Protocol: 13 November 2018**

## *Appendix 16.1.1 Protocol and Protocol Amendments*

THERAPEUTICS
INCORPORATED

December 19, 2018

IntegReview IRB
3815 S. Capital of Texas Highway, Suite 320
Austin, TX 78704

Administrative letter for study FX2018-23

Administrative Amendment #2 to Protocol FX2018-23: A Randomized, Evaluator-Blinded, Bilateral Comparison Study of two Topicals in the Treatment of Subjects with Acne Vulgaris

To whom it may concern:

The purpose of this administrative letter is to clarify the test articles used in this study do not contain minocycline.

Sincerely,

PPD

Senior Clinical Project Manager

PPD

VP, Clinical Development

PPD

THERAPEUTICS INC.
The Dermatology CRO

December 6, 2018

Administrative Amendment # 1

**RE: Administrative Amendment #1 for Foamix Pharmaceuticals, Protocol FX2018-23: A Randomized, Evaluator-Blinded, Bilateral Comparison Study of Two Topicals in the Treatment of Subjects with Acne Vulgaris (IRB approval date: 26-Oct-2018)**

To whom it may concern,

This letter specifies a modification to Protocol FX2018-23 version 2.0 dated 13Nov2018 to change the protocol from a Phase 4 to a Phase 1b protocol as the study drug is not approved yet.

The following specific changes (double strikethrough text: deleted, bold text: added) were made to address the modification:

- Page 4, Synopsis (Study Type): Phase **41b**
- Page 18, Background: This Phase **41b**, Proof of Principle study (FX2018-23) will further evaluate the efficacy and safety of FMX101 hydrophobic oil based vehicle compared to a hydro-alcohol solution based vehicle for the treatment of moderate facial acne vulgaris.

The Sponsor believes these clarifications do not represent a significant change to the protocol, and therefore do not require a formal protocol or informed consent amendment. A copy of this letter will be sent to the sites. We will move forward with the administrative change on December 11, 2018 unless we hear otherwise. We look forward to your timely review and approval. Please contact PPD or by email at PPD with any additional questions.

Sincerely,

PPD

PPD

PPD

# A RANDOMIZED, EVALUATOR-BLINDED, BILATERAL COMPARISON STUDY OF TWO TOPICALS IN THE TREATMENT OF SUBJECTS WITH ACNE VULGARIS

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| **PROTOCOL NUMBER:** | FX2018-23 |
| **TI PROJECT NUMBER:** | 152-11051-401 |
| **ORIGINAL PROTOCOL:** | October 18, 2018 |
| **PROTOCOL VERSION:** | 2.0 |
| **PROTOCOL AMENDMENT #1** | November 13, 2018 |
| **FILENAME:** | 152-11051-401_protocol_13Nov2018_v2.0 |
| **SPONSOR:** | Foamix Pharmaceuticals<br>520 US Highway 22, Suite 204<br>Bridgewater, NJ USA |
| **SPONSOR REPRESENTATIVE:** | PPD |
| **MEDICAL MONITOR:** | PPD<br>Therapeutics, Inc.<br>PPD |
| **PROJECT MANAGER:** | PPD |

24 Hour Emergency Telephone Number
PPD

Therapeutics, Incorporated
PPD

## PROTOCOL APPROVAL

The following individuals approve version 2.0 of the FX2018-23 protocol dated November 13, 2018. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

**Foamix Pharmaceuticals Ltd.:**

Signature: PPD Date: 14NOV2018

PPD
Senior Vice President, R PPD

Signature: PPD Date: 11/14/2018

PPD , M
Director, Clinical Trials

**Therapeutics, Inc. Representative(s):**

Signature PPD Date: 11/13/2018

PPD , PP .
Medical Monitor

Signature: PPD PPD Date: 13-NOV-2018

Vice-President, Clinical Development

Signature: PPD Date: 13-Nov-2018

PPD D.
Senior Principal Biostatistician

**STUDY ACKNOWLEDGEMENT**

I understand this protocol contains information that is confidential and proprietary to Foamix Pharmaceuticals.

I have read this protocol, agree that it contains all the details necessary to conduct the study as described, and will conduct this study following this protocol.

I will provide the contents of this protocol to study staff under my direct supervision that need to know the contents to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the test articles. I will provide the contents of the protocol to the responsible Institutional Review Board(s). These disclosures may be made; providing the contents are not used in any other clinical study and they are not disclosed to any other person or entity without prior written consent from Foamix Pharmaceuticals. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to Foamix Pharmaceuticals of any such disclosure.

I understand the study may be terminated or enrollment suspended at any time by Foamix Pharmaceuticals, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

Any additional information added to this protocol is also confidential and proprietary to Foamix Pharmaceuticals and must be treated in the same manner as the contents of this protocol.

_____
Printed Name of Principal Investigator

_____ _____
Investigator Signature Date

Protocol number: FX2018-23 Site number: _____

## PROTOCOL SYNOPSIS

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| **Title** | A Randomized, Evaluator-Blinded, Bilateral Comparison Study of Two Topicals in the Treatment of Subjects with Acne Vulgaris |
| **Study Type** | Phase 4 |
| **Test Articles** | 1. FMX101 hydrophobic oil based vehicle (Test Article A)<br>2. Hydro-alcohol solution based vehicle (Test Article B) |
| **Study Objective** | To evaluate the safety and efficacy of two topicals in the treatment of acne vulgaris. |
| **Study Design** | Randomized, evaluator-blinded, bilateral comparison |
| **Treatment Groups** | Eligible subjects will be randomized (1:1) to treatment with Test Article A to one side of the face versus Test Article B on the contralateral side. |
| **Duration of Treatment** | Once daily for six weeks. |
| **Duration of Study** | Each subject will participate for approximately seven weeks. |
| **Study Population** | Healthy male or female subjects 9 years of age or older with a clinical diagnosis of symmetric moderate facial acne vulgaris (Grade 3 on the Investigator's Global Assessment [IGA]), ≥16 inflammatory lesions (i.e., papules and pustules) on the face, and no more than two active nodules on the face. |
| **Total Number of Subjects** | Approximately 12 subjects will be enrolled to obtain at least 10 evaluable subjects. |
| **Number of Sites** | One to two sites will participate in the study. |
| **Inclusion Criteria** | To enter the study, a subject must meet the following criteria:<br><br>1. Subject is a healthy male or non-pregnant, non-breastfeeding female 9 years of age or older at the time of consent/assent.<br>2. Subject has provided written informed consent/assent. A subject under 18 years of age must provide written informed assent and be accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at that time to continue study participation.<br>3. Subject has a clinical diagnosis of moderate facial acne vulgaris, with an identical IGA score (IGA Grade 3) on both the right and left side of the face at Visit 1/Baseline.<br>**NOTE: Right or Left side of the face refers to the subject's Right or Left side of his/her face.**<br>4. Subject must have a minimum of 16 inflammatory lesions (papules and pustules) on the face at Visit 1/Baseline. The inflammatory lesion |

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| | count on the right and left side of the face should be similar (defined as within ~ 50% of each other based on the side with the higher lesion count; e.g., if the left side of the face has 17 lesions, then 50% of 17 is 8.5, rounding up to nine (9) lesions; this means that the right side can have as few as eight lesions [17 minus 9]) and have a minimum of eight lesions on each side.<br>5. Subject and parent/guardian (if applicable) are willing and able to apply the test article(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study.<br>6. Subject must be willing and able to refrain from use of all other topical products in the Treatment Area, all acne medications other than test article, and all antibiotics during the study period.<br>7. Subject, in the investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of facial acne vulgaris or otherwise impact the integrity of the study, or exposes the subject to an unacceptable risk by study participation.<br>8. Females must be surgically sterile[1] or use an effective method of birth control.[2,3] Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)[4] at Visit 1/Baseline.<br>9. Subject is willing to use only the supplied non-medicated cleanser and to refrain from use of any other acne medication, medicated cleanser, excessive sun exposure, and tanning booths for the duration of the study. |
| **Exclusion Criteria** | A subject is ineligible to enter the study if he/she meets one or more of the following criteria:<br><br>1. Subject is pregnant, lactating, or is planning to become pregnant during the study.<br>2. Subject has active nodulocystic acne or acne conglobata, acne fulminans, or other forms of acne (e.g., acne mechanica). |

[1] Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment), or bilateral oophorectomy.

[2] Effective forms of birth control include a) hormonal contraceptives [e.g., oral, transdermal, injectable, implantable, or vaginal ring] (see next footnote), b) intrauterine device for at least one week prior to test article application, c) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], d) monogamous relationship with a partner who is sterile [e.g., vasectomy performed at least six months prior to study entry], or e) total abstinence for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.

[3] WOCBP who are currently taking and want to remain on hormonal therapy (e.g., oral, transdermal, injectable, implantable, vaginal ring) must continue treatment per label and must not change their dosing regimen during the study. In addition, WOCBP taking hormonal therapy for any reason (e.g., as contraception, etc.) must be on the same treatment for at least three months prior to study entry. For subjects that do not meet the above requirements; the washout period for hormonal therapy is discontinuation of use at least eight weeks prior to the start of the study.

[4] UPT must have a minimum sensitivity of 25 mIU ß-hCG/mL.

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| | 3. Subject has more than two facial nodules/cysts (where nodule/cyst is defined as an inflammatory lesion greater than or equal to 0.5 cm in size with or without cystic changes) in total with no more than one nodule/cyst per the right or left side of the face.<br>4. Subject has any skin condition that, in the investigator's opinion, could interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneiform eruptions caused by medications, steroid acne, steroid folliculitis, or bacterial folliculitis).<br>5. Subject has folliculitis on the face.<br>6. Subject has excessive facial hair (e.g., beards, sideburns, moustaches) or other facial attributes that, in the investigator's opinion, would interfere with diagnosis or assessment of acne vulgaris.<br>7. Subject has a history of hypersensitivity or allergy to any of the test articles and/or any of the ingredients in the test articles.<br>8. Subject has used the following medications:<br><u>Within one week prior to randomization:</u><br>• Medicated facial cleansers on the face.<br>• Any topical acne treatments on the face.<br><u>Within four weeks prior to randomization:</u><br>• Topical retinoids on the face.<br>• Topical anti-inflammatories and/or corticosteroids on the face.<br>• Topical corticosteroids on body areas other than the face for more than 15 consecutive days and on more than 10% of the body surface area (BSA). In body folds, such as axillary and inguinal regions, only mild topical steroids are allowed for short term use (≤15 consecutive days).<br>• Systemic antibiotics.<br>• Systemic acne treatments.<br><u>Within 12 weeks prior to randomization:</u><br>• Systemic retinoids.<br>• Systemic corticosteroids (Note: Intranasal and inhaled corticosteroids may be used throughout the trial if the subject is on a stable dose [i.e., consistent use over a 4-week period]).<br>9. Subject has used oral contraceptives or estrogen for less than three continuous months prior to Visit 1/Baseline.<br>10. Subject has used a sauna during the two weeks prior to randomization.<br>11. Subject has had epilation of the face within two weeks prior to randomization.<br>12. Subject is planning surgery during the study.<br>13. Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the study.<br>14. Subject is currently enrolled in an investigational drug, device, or biologic study.<br>15. Subject has used an investigational drug or investigational device treatment within 30 days prior to first application of the test article.<br>16. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator. |

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| | 17. Subject and parent/guardian (if applicable) are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.<br>18. Subject has a documented drug addiction or alcohol abuse within the last two years. Heavy drinking levels defined by The Substance Abuse and Mental Health Services Administration 13 as drinking five or more alcoholic drinks on the same occasion on each of five or more days in the past 30 days.<br>19. Subject has a documented history of depression that is not, in the opinion of the investigator, currently adequately controlled with medication. |
| **Study Procedures** | **NOTE: Clinical evaluations (Right and Left Facial IGA and lesion counts) will be performed by a Blinded Evaluator who is not involved in randomization, test article application instructions, or documentation of test article compliance. The same Blinded Evaluator should evaluate a subject over the course of the study.**<br><br>Subjects can be screened for the study up to 45 days before Baseline. During screening, the study requirements will be reviewed, written informed consent/assent obtained, and eligibility confirmed. These procedures may be combined with the Baseline Visit if wash out from prohibited medications is not required. If applicable, qualified subjects can wash out from prohibited acne medications or treatments prior to their Baseline Visit once they have been consented/assented. Subjects who require washout for longer than 45 days will be re-consented/assented.<br><br>The study will consist of a Screening/Baseline Visit and follow-up visits at Weeks 1, 2, 4, 6, and 7. An unscheduled in-office visit may be done at the discretion of the investigator for subjects with tolerability issues or a material adverse event (AE) concern.<br><br>Visit 1 (Day 1): Screening/Baseline. The study requirements and procedures will be reviewed and written informed consent/assent must be obtained prior to the initiation of any study-related procedures. Demographics, inclusion/ exclusion (I/E) criteria, medical history, and concomitant medications and procedures/therapies will be reviewed to determine eligibility. Subjects that require a "washout" period prior to enrollment into the study to meet I/E criteria requirements will be required to return to the clinic within 45 days to complete the remaining activities. Subjects who require "washout" for longer than 45 days will be re-consented. The following procedures will be performed on Day 1: confirmation of eligibility, demographics, medical history, review of concomitant medications and procedures/therapies, dermatologic exam, a UPT for WOCBP, clinical evaluations (Right and Left Facial IGA and lesion counts) by a Blinded Evaluator, Right and Left Facial LSR assessment, and standardized photography of the face. **Note: subjects must have identical IGA scores (IGA Grade 3) on both the Right and Left side of the face at Baseline with similar lesion counts (defined as within ~ 50% of each other and a minimum of eight lesions on each side).** Prior to test article application, transepidermal water loss (TEWL) and sebum assessment will be performed as defined in a separate procedure manual on the Right and Left side of the face. Qualified subjects will be |

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| | randomly assigned to one of two test articles on one side with the other test article on the contralateral side. Test article application will be demonstrated by the study staff using test article supplied to the site. Test article(s) will be dispensed along with application instructions, and a Subject Diary will be provided to document applied or missed doses. Subjects will apply the first doses of the test article in the clinic under staff supervision to ensure proper application. Subjects will be instructed to apply the test article once daily in the evening for six weeks. LSRs will be assessed 15 minutes following test article application. AEs will be documented; AEs on the face will be segmented by Right or Left, if applicable. The subject will be scheduled for their next follow-up visit.<br><br>Visit 2 (Week 1): Follow-up 1, Visit 3 (Week 2): Follow-up 2, and Visit 4 (Week 4): Follow-Up 3. The subject will return to the clinic for review of concomitant medications and procedures/therapies. Clinical evaluations (IGA and lesion counts for the Right and Left side of the face) will be performed by a Blinded Evaluator. LSRs will be assessed for the Right and Left side of the face. **Visit 3 and Visit 4 only: standardized photographs will be taken. TEWL and sebum assessment will be performed as defined in a separate procedure manual on the Right and Left side of the face.** The Subject Diary will be reviewed/collected/distributed as necessary and test article will be returned/weighed and compliance (Right vs Left) will be reviewed; the site staff will remind the subject to continue to apply test article daily (once in the evening) until the next clinic visit and to not apply test article or other products (including make-up and using a cleanser) to the face within four hours of the next clinic visit. Test article application will be demonstrated at each clinic visit – emphasizing the importance to properly apply the test articles to the correct side of the face. Additional test article will be dispensed as needed. AEs will be documented; AEs on the face will be segmented by Right or Left, if applicable. The subject will be scheduled for the next visit.<br><br>Visit 5 (Week 6): End of Treatment (EOT). The subject will return to the clinic for review of concomitant medications and procedures/therapies. A UPT for WOCBP will be performed as applicable. Clinical evaluations (IGA and lesion counts for the Right and Left side of the face) will be performed by a Blinded Evaluator. LSRs will be assessed for the Right and Left side of the face. Standardized photos will be taken. TEWL and sebum assessment will be performed as defined in a separate procedure manual on the Right and Left side of the face. Test article accountability will be documented; all test articles and subject diaries will be collected. AEs will be documented; AEs on the face will be segmented by Right or Left, if applicable. The subject will be scheduled for the next visit.<br><br>Visit 6 (Week 7): End of Study (EOS). The subject will return to the clinic for review of concomitant medications and procedures/therapies. Clinical evaluations (IGA and lesion counts for the Right and Left side of the face) and LSRs will be performed on the Right and Left side of the face. TEWL and sebum assessment will be performed as defined in a separate procedure manual on the Right and Left side of the face. AEs will be documented; AEs on the face will be segmented by Right or Left, if applicable. Any new or |

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| | ongoing treatment emergent AEs (TEAEs) at the EOT visit (Visit 5) will also be evaluated. The subject will exit the study.<br><br>Unscheduled Visit. The investigator may see the subject at an unscheduled visit to manage any AEs or LSRs (if applicable). The subject will return to the clinic for review of concomitant medications and procedures/therapies, LSRs, and AEs. Test article accountability will be documented. The Subject Diary and test article compliance will be reviewed. All assessments will take into account potential differences between the Right and Left side of the face. The subject's next appointment will be confirmed. |
| **Study Measurements** | Dosing Compliance:<br>Measures of test article compliance will include the duration (days) of treatment (defined as last dose date – first dose date +1), the total number of applications applied and missed (determined from the doses reported in the Subject Diary), and the percent of expected doses applied. A subject will be considered compliant with the dosing regimen if the subject applies at least CCI and no more than CCI of the expected test article applications for the specified duration of the study for all Test Articles and does not miss the scheduled applications for more than three consecutive days.<br><br>Efficacy and safety measurements will be assessed according to the schedule of events.<br><br>Efficacy:<br>*Investigator's Global Assessment (Right and Left Face)*<br>Overall severity of acne will be assessed using a five-point scale where 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, and 4=Severe. This is a static morphological scale that refers to a point in time and not a comparison to Baseline.<br><br>*Acne Lesion Counts (Right and Left Face)*<br>The number of non-inflammatory lesions (open and closed comedones) and inflammatory lesions (papules and pustules) on the face (including those present on the nose) will be counted. Counts of nodules and cysts will be reported separately and are not to be included in the inflammatory or non-inflammatory lesion counts.<br><br>*VISIA (Right and Left Face)*<br>Digital photographs will be taken of the face with the VISIA (Canfield Scientific) to document the progress of the subject (right vs left sides) in the study at Visit 1/Baseline, Visit 3, Visit 4, and Visit 5/EOT. At the election of the Sponsor, they may choose to perform an independent separate analysis of the photographs for clinical changes relative to Baseline.<br><br>*Bioinstrumentation Assessments (Right and Left Face)*<br>TEWL and sebum measurements will be taken as specified per protocol.<br><br>Safety:<br>*Adverse Events (segmented to Right vs Left Face application area, as/if appropriate)* |

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| | All reported or observed AEs will be recorded. At each visit, subjects will also be questioned specifically about the status of any ongoing AEs. Untoward events that occur prior to the first dose of test article will be captured in the Medical History section of the case report form (CRF) unless they are related to a study-specific procedure.<br><br>*Local Skin Reactions (Right and Left Face)*<br>At each visit, LSRs (erythema, edema, scaling/dryness, burning/stinging, pruritus, erosion, and pain) will be assessed. Erythema, edema, scaling/dryness, and erosion will be assessed by the investigator and burning/stinging, pain, and pruritus will be assessed by the subject. Assessments will be made using a 4-point ordinal scale where 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). Only LSRs that require medical intervention (e.g., prescription medication), require withholding or discontinuation of the application of the test article, or extend 2 cm beyond the Treatment Area will be documented as AEs. Any LSRs that are not listed above will be recorded as an AE.<br><br>*Urine Pregnancy Tests*<br>A UPT will be performed at Visit 1/Baseline and at Visit 5/Week 6/EOT for WOCBP. |
| **Study Endpoints** | <u>Efficacy Endpoints:</u><br>• IGA Assessment<br>  o IGA within subject Test Article A versus Test Article B – at Week 6; Test Article A > Test Article B, Test Article A = Test Article B, Test Article A < Test Article B.<br>  o IGA scores will be dichotomized to "success" or "failure" where "success" is defined as at least a two-point improvement in IGA score relative to Baseline, Test Article A versus Test Article B.<br>• Absolute and Percent Change from Baseline to Week 6 in the inflammatory (papules and pustules) lesion count, within subject Test Article A versus Test Article B.<br>• Absolute and Percent Change from Baseline to Week 6 in the non-inflammatory (open and closed comedones) lesion count, within subject Test Article A versus Test Article B.<br>• Sebum and TEWL assessments relative to Baseline versus Weeks 2, 4, 6 and 7, within subject Test Article A versus Test Article B.<br>• VISIA Digital Photographs may undergo an independent separate analysis for clinical changes relative to Baseline.<br><br><u>Safety Endpoints:</u><br>• Incidence (severity and causality) of any reported or observed TEAEs, whether or not they are considered to be related to the test article [Note: all application site AEs will be analyzed for Test Article A vs Test Article B involvement].<br>• Number of subjects with improved/same versus worsened severities compared to Baseline of the following LSRs: erythema, |

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| | edema, scaling/dryness, burning/stinging, pruritus, erosion, and pain at each time point, Test Article A vs Test Article B. |
| **Sample Size Calculations** | This is a pilot proof of principle study, as such no specific power calculations were used to establish the sizing of this study. |
| **Statistical Methods** | All statistical processing will be performed using SAS® Version 9.4 unless otherwise stated.<br><br>**Study Populations:**<br>The Safety population will include all randomized subjects who received test article and applied at least one application.<br><br>The modified intent-to-treat (mITT) population will include all randomized subjects who met all I/E criteria, applied at least one dose of test article, and returned for at least one post-Baseline evaluation visit.<br><br>The per-protocol (PP) population will include all randomized subjects who met all mITT population criteria, were compliant with the assigned test articles based on the subject diaries (applied at least CCI and no more than CCI of the expected test article applications for the specified duration of the study), did not miss the scheduled test article applications for more than three consecutive days (i.e., three consecutive days with no test article application), have no other evidence of material dosing noncompliance, and completed the primary endpoint evaluation at Week 6 within the designated visit window (±3 days) with no significant protocol violations and prohibited medications that would affect the treatment evaluation.<br><br>**Dosing Compliance**:<br>As appropriate, outcomes relative to Test Article A vs Test Article B will be tabulated. Descriptive statistics will be used to summarize test article compliance for each analysis population. Compliant subjects are defined as those who apply at least CCI and no more than CCI of the expected test article applications (Right and Left face), and did not miss scheduled applications for more than three consecutive days. The percentage of compliant subjects will also be presented.<br><br>**Efficacy Analyses:**<br>As appropriate outcomes relative to the Test Article A vs Test Article B will be tabulated for all visits. The efficacy analyses conducted on the mITT and PP populations will be compiled using descriptive statistics only for all efficacy variables.<br><br>**Safety Analyses:**<br>As appropriate, outcomes relative to the Test Article A vs Test Article B will be tabulated. All safety analyses will be performed in the Safety population unless otherwise stated.<br><br><u>Adverse Events</u><br>All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percent of unique subjects reporting each TEAE will be summarized by MedDRA system |

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| | organ class (SOC), MedDRA preferred term (PT), and treatment group. AEs will also be similarly summarized by SOC, PT, maximum severity, and treatment group as well as by SOC, PT, and closest relationship to test article. Application site AEs will be summarized separately by treatment group. All AEs reported during the study will be listed.<br><br><u>Local Skin Reactions</u><br>The frequency of the individual LSRs (erythema, edema, scaling/dryness, burning/stinging, pruritus, erosion, and pain) will be tabulated by severity and treatment group at each onsite clinic visit. Subject counts for improved/same versus worsened compared to Baseline value will be also presented for the post-baseline visits. |

## SCHEDULE OF EVENTS

| Visit | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Unscheduled Visit |
|---|---|---|---|---|---|---|---|
| | Screening/ Baseline | Week 1 / Follow – up 1 | Week 2 / Follow – up 2 | Week 4 / Follow – up 3 | Week 6 / EOT[1] | Week 7 / EOS | |
| Days | 1 | 8 ± 2 | 15 ± 3 | 29 ± 3 | 43 ± 3 | 50 ± 3 | |
| Informed Consent/Assent[2] | X | | | | | | |
| Demographics | X | | | | | | |
| Eligibility | X | | | | | | |
| Medical History | X | | | | | | |
| Concomitant Medications and Procedures/Therapies | X | X | X | X | X | X | X |
| Dermatological Exam | X | | | | | | |
| UPT[3] for WOCBP[4] | X | | | | X | | |
| Clinical Evaluations (IGA and lesion counts, R vs L)[5] | X | X | X | X | X | X | |
| LSR Assessment, R vs L | X[6] | X | X | X | X | X | X |
| VISIA Photography | X | | X | X | X | | |
| TEWL/Sebum, R vs L | X | | X | X | X | X | |
| Randomization | X | | | | | | |
| Test Article Accountability, R vs L | X | X | X | X | X | | X |
| Demonstrate how to apply test articles[7] | X | X | X | X | | | |
| Apply test articles | X | | | | | | |
| Subject Diary and Compliance Review[8]: Dispense (D), Review (R), and/or Collect (C) | D | C+R+D | C+R+D | C+R+D | C+R | | C+R+D, as necessary |
| Adverse Events | X[9] | X | X | X | X | X | X |

[1] Or early termination from the study.
[2] Consent/assent may be performed up to 45 days prior to Baseline. Subjects who require "washout" for longer than 45 days will be re-consented.
[3] UPTs must have a minimum sensitivity of 25 mIU ß-hCG/mL.
[4] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
[5] Clinical grading to be done by the same Blinded Evaluator.
[6] LSRs will be assessed both before and 15 minutes following test article application.
[7] Study staff will provide a Subject Instruction Sheet to the subject and parent/guardian (if applicable) and test article application will be demonstrated using the test article samples provided to the site.
[8] Review Subject Diary and amount of test article used since last visit to determine subject compliance. Re-educate subject on use of the test article with particular attention to inappropriate prior use of test article – be it amount of product applied and/or frequency of use.
[9] Recorded under Medical History.

## ABBREVIATIONS

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| AE | Adverse Event |
| β-hCG | Beta-Human Chorionic Gonadotropin |
| BSA | Body Surface Area |
| CLIA | Clinical Laboratory Improvement Amendments |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| EOS | End of Study |
| EOT | End of Treatment |
| FDA | Food and Drug Administration |
| IB | Investigator Brochure |
| I/E | Inclusion/Exclusion |
| IGA | Investigator's Global Assessment |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| L | Left |
| LSR | Local Skin Reaction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mL | Milliliter |
| mIU | Milli International Units |
| mITT | Modified Intent-to-Treat |
| PP | Per-Protocol |
| PT | Preferred Term |
| R | Right |
| SAE | Serious Adverse Event |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Events |
| TEWL | Transepidermal Water Loss |
| TI | Therapeutics, Incorporated |
| UPT | Urine Pregnancy Test |
| USP | United States Pharmacopeia |
| WHO | World Health Organization |
| WOCBP | Women of Childbearing Potential |

**TABLE OF CONTENTS**

## 1. BACKGROUND

Acne vulgaris is a common disease of both males and females, usually manifesting initially during adolescence. The primary pathologic events are initiated in the pilosebaceous units, especially of sebaceous-gland-bearing areas of the face, chest, and back as a result of increased androgen stimulation initiated at adrenarche or puberty. As a result of both abnormal keratinization of the infra-infundibular portion of the pilosebaceous follicle and increased sebum produced in the gland, a blockage of the duct results in the unapparent clinical lesion of the microcomedone. Continued blockage, colonization of the follicle by *Propionibacterium acnes*, and generation of multiple chemoattractant and proinflammatory moieties may result in non-inflammatory clinical lesions, comedones, and inflammatory lesions: papules, pustules, nodules, and cysts [1].

FMX101 4% is a minocycline containing topical foam being developed as a treatment for acne vulgaris. Foamix has conducted three Phase 3 studies (FX2014-04; FX2014-05, and FX2017-22) to assess the safety and tolerability of FMX101 4%, which contains minocycline and the vehicle being studied. The treatment has been shown to be effective and well-tolerated. This Phase 4, Proof of Principle study (FX2018-23) will further evaluate the efficacy and safety of FMX101 hydrophobic oil based vehicle compared to a hydro-alcohol solution based vehicle for the treatment of moderate facial acne vulgaris.

## 2. RATIONALE

FMX101 vehicle is an oil-based formulation that may have a role in the effectiveness and tolerance of the FMX101 4% minocycline acne treatment. This Proof of Principle trial will study two formulations: the FMX101 vehicle versus a topical hydro-alcohol formulation, for safety and efficacy in the treatment of acne vulgaris.

## 3. OBJECTIVE

The objective of this study is to evaluate the safety and efficacy of the two topical formulations in acne vulgaris subjects. More specifically, the above formulations will be compared for their effect on facial sebum.

## 4. STUDY DESIGN

This is a randomized, evaluator-blinded, bilateral comparison study of FMX101 hydrophobic oil based vehicle (Test Article A) and hydro-alcohol solution based vehicle (Test Article B) in healthy male or female subjects 9 years of age or older with facial acne vulgaris. Eligible subjects must have a clinical diagnosis of symmetric moderate facial acne vulgaris (Grade 3 on the Investigator's Global Assessment [IGA]) and ≥16 inflammatory lesions (i.e., papules and pustules) on the face. Approximately 12 subjects will be enrolled to obtain about 10 evaluable subjects at one to two study sites. Subjects will be randomized (1:1) to treatment with Test Article A to one side of the face versus Test Article B on the contralateral side.

1. FMX101 hydrophobic oil based vehicle (Test Article A)
2. Hydro-alcohol solution based vehicle (Test Article B)

Subjects will be instructed to apply the assigned test articles once daily in the evening for six weeks to the appropriate sides of the face. The study will consist of a Screening/Baseline Visit, Visits at Week 1, Week 2, and Week 4, along with a Week 6/End of Treatment (EOT) Visit, and a Week 7/End of Study (EOS) Visit. An unscheduled in-office visit may be completed at the discretion of the investigator for subjects with tolerability issues or a material adverse event (AE) concern. Efficacy measurements will include IGA, lesion counts, Transepidermal Water Loss (TEWL) and sebum measurements, and VISIA photographs. Safety measurements will include assessments of local skin reactions (LSRs), documentation of AEs, and a urine pregnancy test (UPT) for women of child-bearing potential (WOCBP).

# 5. STUDY POPULATION

## 5.1 Subject Eligibility

To be included in the study, subjects must meet the following inclusion and none of the exclusion criteria.

### *5.1.1 Inclusion Criteria*

1. Subject is a healthy male or non-pregnant, non-breastfeeding female 9 years of age or older at the time of consent/assent.
2. Subject has provided written informed consent/assent. A subject under 18 years of age must provide written informed assent and be accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at that time to continue study participation.
3. Subject has a clinical diagnosis of moderate facial acne vulgaris, with an identical IGA score (IGA Grade 3) on both the right and left side of the face at Visit 1/Baseline.

   **NOTE: Right or Left side of the face refers to the subject's Right or Left side of his/her face.**
4. Subject must have a minimum of 16 inflammatory lesions (papules and pustules) on the face at Visit 1/Baseline. The inflammatory lesion count on the right and left side of the face should be similar (defined as within ~ 50% of each other based on the side with the higher lesion count; e.g., if the left side of the face has 17 lesions, then 50% of 17 is 8.5, rounding up to nine (9) lesions; this means that the right side can have as few as eight lesions [17 minus 9]) and have a minimum of eight lesions on each side.

5. Subject and parent/guardian (if applicable) are willing and able to apply the test article(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study.
6. Subject must be willing and able to refrain from use of all other topical products in the Treatment Area, all acne medications other than test article, and all antibiotics during the study period.
7. Subject, in the investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of facial acne vulgaris or otherwise impact the integrity of the study, or exposes the subject to an unacceptable risk by study participation.
8. Females must be surgically sterile[5] or use an effective method of birth control.[6,7] WOCBP must have a negative UPT[8] at Visit 1/Baseline.
9. Subject is willing to use only the supplied non-medicated cleanser and to refrain from use of any other acne medication, medicated cleanser, excessive sun exposure, and tanning booths for the duration of the study.

### *5.1.2 Exclusion Criteria*

1. Subject is pregnant, lactating, or is planning to become pregnant during the study.
2. Subject has active nodulocystic acne or acne conglobata, acne fulminans, or other forms of acne (e.g., acne mechanica).
3. Subject has more than two facial nodules/cysts (where nodule/cyst is defined as an inflammatory lesion greater than or equal to 0.5 cm in size with or without cystic changes) in total with no more than one nodule/cyst per the right or left side of the face.
4. Subject has any skin condition that, in the investigator's opinion, could interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneiform eruptions caused by medications, steroid acne, steroid folliculitis, or bacterial folliculitis).

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[5] Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment), or bilateral oophorectomy.

[6] Effective forms of birth control include a) hormonal contraceptives [e.g., oral, transdermal, injectable, implantable, or vaginal ring] (see next footnote), b) intrauterine device for at least one week prior to test article application, c) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], d) monogamous relationship with a partner who is sterile [e.g., vasectomy performed at least six months prior to study entry], or e) total abstinence for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.

[7] WOCBP who are currently taking and want to remain on hormonal therapy (e.g., oral, transdermal, injectable, implantable, vaginal ring) must continue treatment per label and must not change their dosing regimen during the study. In addition, WOCBP taking hormonal therapy for any reason (e.g., as contraception, etc.) must be on the same treatment for at least three months prior to study entry. For subjects that do not meet the above requirements; the washout period for hormonal therapy is discontinuation of use at least eight weeks prior to the start of the study.

[8] UPT must have a minimum sensitivity of 25 mIU ß-hCG/mL.

5. Subject has folliculitis on the face.
6. Subject has excessive facial hair (e.g., beards, sideburns, moustaches) or other facial attributes that, in the investigator's opinion, would interfere with diagnosis or assessment of acne vulgaris.
7. Subject has a history of hypersensitivity or allergy to any of the test articles and/or any of the ingredients in the test articles.
8. Subject has used the following medications:
   Within one week prior to randomization:
   - Medicated facial cleansers on the face.
   - Any topical acne treatments on the face.

   Within four weeks prior to randomization:
   - Topical retinoids on the face.
   - Topical anti-inflammatories and/or corticosteroids on the face.
   - Topical corticosteroids on body areas other than the face for more than 15 consecutive days and on more than 10% of the body surface area (BSA). In body folds, such as axillary and inguinal regions, only mild topical steroids are allowed for short term use (≤15 consecutive days).
   - Systemic antibiotics.
   - Systemic acne treatments.

   Within 12 weeks prior to randomization:
   - Systemic retinoids.
   - Systemic corticosteroids (Note: Intranasal and inhaled corticosteroids may be used throughout the trial if the subject is on a stable dose [i.e., consistent use over a 4-week period]).
9. Subject has used oral contraceptives or estrogen for less than three continuous months prior to Visit 1/Baseline.
10. Subject has used a sauna during the two weeks prior to randomization.
11. Subject has had epilation of the face within two weeks prior to randomization.
12. Subject is planning surgery during the study.
13. Subject has the need or plans to be exposed to artificial tanning devices or excessive sunlight during the study.
14. Subject is currently enrolled in an investigational drug, device, or biologic study.
15. Subject has used an investigational drug or investigational device treatment within 30 days prior to first application of the test article.
16. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.
17. Subject and parent/guardian (if applicable) are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
18. Subject has a documented drug addiction or alcohol abuse within the last two years. Heavy drinking levels defined by The Substance Abuse and Mental Health Services Administration 13 as drinking five or more alcoholic drinks on the same occasion on each of five or more days in the past 30 days.

19. Subject has a documented history of depression that is not, in the opinion of the investigator, currently adequately controlled with medication.

### *5.1.3 Subject Withdrawal Criteria*

Procedures for handling subjects who are discontinued from the study are described in Section 13.2. Subjects who are discontinued will not be replaced.

## 6. TEST ARTICLES AND REGIMEN

The test articles used in this study are described below.

### 6.1 Description

| | |
|---|---|
| Test Article A: | FMX101 hydrophobic oil based vehicle |
| Other ingredients: | soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (also known as beeswax), stearyl alcohol, and docosanol (also known as behenyl alcohol). The propellant is a mixture of butane, isobutane, and propane. |
| Test Article B: | Hydro-alcohol solution based vehicle |
| Other ingredients: | water, alcohol denatured, butylene glycol, poloxamer 124, lactic acid, PEG-40 hydrogenated castor oil, sodium hydroxide, glyceryl caprylate, phenoxyethanol, and fragrance. |

### 6.2 Instructions for Use and Application

At Visit 1/Baseline, subjects will be instructed on how to apply the test articles and will apply the first test article applications at the site under supervision of the study staff. Subjects will be instructed to apply the test articles to the appropriate sides of the face once daily in the evening at approximately the same time for six weeks.

**NOTE: Since this is a bilateral comparison study of two test articles, it is important that the same product be applied to the same side of the face over the six week treatment period.** CCI [redacted]

CCI [redacted]

**To minimize errors, at each clinic visit during the treatment period the study staff must review and emphasize the proper application of the test articles.**

Subjects will be provided with a Subject Instruction Sheet detailing how to apply the test articles (see Appendix 1) and a Subject Diary (see Appendix 2) to record dates and times of applications. Subjects will be instructed to bring all test article containers (used and unused) and the Subject Diary to the study visits. At the appropriate study visits, test article containers will be weighed and the Subject Diary will be collected, reviewed, and a new one will be dispensed to the subject (as needed). Subjects will be instructed to store the test articles according to the directions on the label. Subjects will also be instructed not to apply the test articles four hours before any study visit.

### 6.3 Warnings, Precautions, and Contraindications

These test articles are for topical use only. Care should be taken to avoid contact with eyes and all mucous membranes. If contact with eyes occurs, rinse thoroughly with water.

Subjects with a known sensitivity to any of the ingredients in the test articles should not participate in this study.

Should a significant skin irritation or rash develop, discontinue use.

In case of accidental ingestion, subjects should contact the investigator immediately.

The effects of the test article in nursing mothers, pregnant women, and their unborn children are unknown. WOCBP must not be pregnant or planning a pregnancy during the study period.

## 7. RANDOMIZATION ASSIGNMENT

Each subject will be randomized to the two treatment options on a 1:1 basis with one product (e.g. Test Article A) to one side of the face and the other product (e.g. Test Article B) to the contralateral side of the face.

1. FMX101 hydrophobic oil based vehicle (Test Article A)
2. Hydro-alcohol solution based vehicle (Test Article B)

**NOTE: Right or Left side of the face refers to the subject's Right or Left side of his/her face with respect to which side of the face a given Test Article should be applied.**

## 8. PRIOR AND CONCOMITANT THERAPIES

Current medications and any medications taken within 30 days prior to the start of the study (Visit 1/Baseline) will be recorded as prior/concomitant medications with the dose and corresponding indication. The medications to be recorded include prescription, over-the-counter medications, and vitamins, minerals, and dietary supplements being taken for a therapeutic indication. Vitamins and mineral supplements are permitted at dosages

considered by the investigator as reasonable for maintaining good health and will not be recorded in the case report forms (CRFs). All concomitant medications will be coded with the current version of the WHO Drug Dictionary.

Any changes in concomitant medications and/or therapies/procedures during the study must be recorded. The reason for any changes in concomitant medications and/or therapies/procedures should be reported and should reflect either a baseline medical condition documented in the medical history or in conjunction with an AE.

### 8.1 Prohibited Medications or Therapies

Prior to entry in the study or during the course of the study, subjects must not use the medications or procedures within the time frame prior to randomization as specified in Section 5.1.2. Subjects may washout from prohibited medications or treatments for acne vulgaris. The following medications and procedures/therapies are prohibited during the study from Visit 1/Baseline through Visit 6/EOS:

- The use of oral contraceptives or estrogen when initiated during the study or when initiated for less than three continuous months prior to Visit 1/Baseline
- Any investigational drug, device, or biologic within 30 days prior to first application of the test article
- Any planned surgeries
- Artificial tanning devices or excessive sunlight during the study

Within one week prior to randomization:
- Medicated facial cleansers on the face
- Any topical acne treatments on the face

Within two weeks prior to randomization
- Epilation of the face
- Use of a sauna

Within four weeks prior to randomization:
- Topical retinoids on the face
- Topical anti-inflammatories and/or corticosteroids on the face
- Topical corticosteroids on body areas other than the face for more than 15 consecutive days and on more than 10% of the BSA. In body folds, such as axillary and inguinal regions, only mild topical steroids are allowed for short term use (≤15 consecutive days)
- Systemic antibiotics
- Systemic acne treatments

Within 12 weeks prior to randomization

- Systemic retinoids
- Systemic corticosteroids (NOTE: Intranasal and inhaled corticosteroids use prior to Baseline may be used throughout the trial if the subject is on a stable dose, defined as continuous use in a dose regimen similar to the 4-week period prior to Baseline)

## 8.2 Allowed Medications or Therapies

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Non-prohibited chronic therapies being used at Visit 1/Baseline may be continued, but must be recorded.

Effective methods of contraception for WOCBP are required per Inclusion Criterion #8, but subjects must be using the same method for at least three continuous months prior to Visit 1/Baseline.

Estrogen therapy is allowed, but subjects must be on estrogen for at least three continuous months prior to Visit 1/Baseline.

Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health; such vitamins and minerals will be recorded in the CRFs if taken for a therapeutic indication or in the source documents only if taken for general health.

Minimal use of make-up (e.g., lip stick, mascara, eye shadow) is permitted after test article application and a one hour dry-down period. These do not need to be recorded in the CRFs.

Intranasal, inhaled, and ophthalmic steroids used for the management of allergies, pulmonary disorders, or other conditions exclusive of acne are permitted. However, those using intranasal, inhaled steroid on a stable dose prior to Baseline shall continue dosing during the study. Medications not intended for or beneficial for the treatment of acne may be used unless specifically excluded or prohibited by this protocol (see Section 8.1), which includes non-prohibited chronic therapies being used at Visit 1/Baseline.

Sunscreens on the face are discouraged during the study given they can potentially affect skin disease. Ideally, wearing a hat is recommended. Nonetheless, when extenuating circumstances warrant sunscreen use, it may be used but should be recorded as a concomitant medication.

# 9. STUDY PROCEDURES

Responsibilities of the Unblinded and Blinded Evaluators are summarized in the Table below: NOTE: To preserve the blinding in the study the Blinded Evaluator must not

participate in any of the obligations of the Unblinded Evaluator. Similarly the Blinded Evaluator must not have access to CRFs for the activities of the Unblinded Evaluator:

| **Table of Responsibilities** | |
|---|---|
| **Unblinded Evaluator** | **Blinded Evaluator** |
| **Tasks to be completed by the same person throughout the study[1]**<br>• AEs and serious AEs (SAEs) and any required management<br>• All LSR Assessments | **Tasks to be completed by the same person throughout the study[1]**<br>• Clinical Evaluations (Right vs Left Facial IGA and lesion counts) |
| **Unblinded Evaluator or Qualified Designee[2]** | **Study Staff** |
| • Concomitant Medications & Procedures / Therapies<br>• Dermatological Exam<br>• Urine Pregnancy Tests<br>• VISIA Photography<br>• TEWL/Sebum Assessment, Right vs Left<br>• Randomization<br>• Test Article Accountability<br>• Demonstrate how to apply test articles<br>• Subject Diary and Compliance Review | **General procedures that may be performed by either blinded or unblinded qualified members of the research staff**<br>• Informed Consent/Assent<br>• Demographics<br>• Eligibility<br>• Medical History |

[1] The same Blinded and Unblinded Evaluators should complete these evaluations for a given subject throughout the study. If this becomes impossible, an appropriately qualified evaluator with overlapping experience with the subject and the study should complete the evaluations. The same person may not complete the evaluations for both the Unblinded and Blinded Evaluator.
[2] Assessments can be performed by different unblinded, qualified individuals for a given subject, throughout the study.

Specific activities for each study visit are listed below.

### 9.1 Visit 1 (Day 1): Screening/Baseline

**Prior to the start of this visit, Study Staff, the Unblinded Evaluator, and subjects will be reminded not to discuss the treatment, side effects, or study experience with the Blinded Evaluator.**

*At Screening, the Unblinded Evaluator or designee will:*

- Obtain a signed, written informed consent/assent.
- Record demographics.
- Confirm I/E criteria.

- Record medical history.
- Record prior and/or concomitant medications and procedures/therapies.

*If the subject requires washout from previous medications, the remaining activities will be performed after washout is complete.*

- Perform a dermatological exam of the head. Record abnormalities in medical history.
- Perform a UPT for all WOCBP. The results must be negative for the subject to be enrolled.
- **Must be performed by a Blinded Evaluator:** Perform clinical evaluations (IGA and lesion counts, R vs L). See Section 10.1 and Section 10.2.
- Assess LSRs on the Right and Left sides of the face separately prior to first test article applications. See Section 10.5.2.
- Perform VISIA photography. See Section 10.3.
- Perform TEWL and sebum assessments. See Section 10.4.
- Assign the subject the next available (lowest) subject number in ascending order and randomize the subject.
- Review and dispense a Subject Instruction Sheet (see Appendix 1).
- Dispense the Subject Diary and provide completion instructions (see Appendix 2).
- Document Test Article Accountability.
- Demonstrate proper test article applications and supervise the first applications in the clinic.
- Assess LSRs on the Right and Left sides of the face separately 15 minutes after the first application of the test articles.
- Record any AEs.
- Schedule a follow-up visit.

### 9.2 Visit 2 (Day 8 ± 2): Week 1/Follow-up 1, Visit 3 (Day 15 ± 3): Week 2/Follow-up 2, and Visit 4 (Day 29 ± 3): Week 4/Follow-up 3

**Prior to the start of this visit, Study Staff, the Unblinded Evaluator, and subjects will be reminded not to discuss the treatment, side effects, or study experience with the Blinded Evaluator.**

*At this visit, the Unblinded Evaluator or designee will:*

- Query the subject for any changes in health status since the previous visit, including concomitant medications and procedures/therapies, and document the findings.
- **Must be performed by a Blinded Evaluator:** Perform clinical evaluations (IGA and lesion counts, R vs L). See Section 10.1 and Section 10.2.
- Assess LSRs on the Right and Left sides of the face separately. See Section 10.5.2.
- **At Visit 3 and Visit 4:**
  - Perform VISIA photography. See Section 10.3.
  - Perform TEWL and sebum assessments. See Section 10.4.

- Document Test Article Accountability, weigh the test article, and collect/dispense the test article, as applicable.
- Demonstrate proper application of the test articles.
- Review compliance and collect/dispense the Subject Diary, as applicable.
- Document any AEs.
- Schedule the next visit.

### 9.3 Visit 5 (Day 43 ± 3): Week 6/End of Treatment

**Prior to the start of this visit, Study Staff, the Unblinded Evaluator, and subjects will be reminded not to discuss the treatment, side effects, or study experience with the Blinded Evaluator.**

*At this visit, the Unblinded Evaluator or designee will:*

- Query the subject for any changes in health status since the previous visit, including concomitant medications and procedures/therapies, and document the findings.
- Perform a UPT for all WOCBP. Any positive results must be followed.
- **Must be performed by a Blinded Evaluator:** Perform clinical evaluations (IGA and lesion counts, R vs L). See Section 10.1 and Section 10.2.
- Assess LSRs on the Right and Left sides of the face separately. See Section 10.5.2.
- Perform VISIA photography. See Section 10.3.
- Perform TEWL and sebum assessments. See Section 10.4.
- Document Test Article Accountability, weigh the test article, and collect the test article.
- Review compliance and collect the Subject Diary.
- Document any AEs.
- Schedule the next visit.

### 9.4 Visit 6 (Day 50 ± 3): Week 7/End of Study

**Prior to the start of this visit, Study Staff, the Unblinded Evaluator, and subjects will be reminded not to discuss the treatment, side effects, or study experience with the Blinded Evaluator.**

*At this visit, the Unblinded Evaluator or designee will:*

- Query the subject for any changes in health status since the previous visit, including concomitant medications and procedures/therapies, and document the findings.
- **Must be performed by a Blinded Evaluator:** Perform clinical evaluations (IGA and lesion counts, R vs L). See Section 10.1 and Section 10.2.
- Assess LSRs on the Right and Left sides of the face separately. See Section 10.5.2.
- Perform TEWL and sebum assessments. See Section 10.4.
- Document any AEs.
- The subject will exit the study.

### 9.5 Unscheduled Visit

**Prior to the start of this visit, Study Staff, the Unblinded Evaluator, and subjects will be reminded not to discuss the treatment, side effects, or study experience with the Blinded Evaluator.**

*At this visit, the Unblinded Evaluator or designee will:*

- Query the subject for any changes in health status since the previous visit, including concomitant medications and procedures/therapies, and document the findings.
- Assess LSRs on the Right and Left sides of the face separately. See Section 10.5.2.
- Document Test Article Accountability, weigh the test article, and collect/dispense the test article, as applicable.
- Review compliance and collect/dispense the Subject Diary, as applicable.
- Document any AEs.

## 10. CLINICAL EVALUATIONS

The following clinical evaluations will be performed according to the schedules indicated during the study. The same investigator should complete the evaluations for a given subject throughout the study. If this becomes impossible a sub-investigator with overlapping experience with the subject and the study should complete the evaluations.

**Clinical evaluations (Right and Left Facial IGA and lesion counts) will be performed by a Blinded Evaluator who is not involved in randomization, test article application instructions, or documentation of test article compliance. The same Blinded Evaluator should evaluate a subject over the course of the study. The study staff, the Unblinded Evaluator, and subjects will also be instructed not to discuss the treatment, AEs, SAEs, or any study experiences with the Blinded Evaluator.**

**The Blinded Evaluator will only have access to the page in the CRF required to document the Right and Left Facial IGA and lesion counts; all other CRF content will be inaccessible.**

### 10.1 Investigator's Global Assessment

The IGA score is a static evaluation of the overall severity or "average" degree of severity of a subject's disease by the Blinded Evaluator, taking into account all of the subject's facial acne lesions as the subject appears on the day of the evaluation. The investigator should NOT refer to any other assessments to assist with this evaluation and should complete the IGA score prior to performing lesion counts. This evaluation is NOT a comparison with the IGA at any other visit or a mathematical calculation based on counts of individual lesion types. Overall severity of acne will be assessed using a five-point scale from 0=Clear to 4=Severe. Subjects must have an identical IGA score of moderate severity (IGA Grade 3) on both the right and left side of the face at Baseline.

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

### 10.2 Acne Lesion Counts

The number of non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules), and nodulocystic lesions (nodules and cysts) on the face (including those present on the nose) will be counted by the Blinded Evaluator. Subjects must have a minimum of 16 inflammatory lesions AND ≤ 2 nodulocystic lesions on the face in total (with no more than one nodule/cyst per the right or left side of the face) at Visit 1/Baseline.

At Visit 1/Baseline, the inflammatory lesion count on the right and left side of the face should be similar (defined as within ~ 50% of each other). For example, if the left side of the face has 17 lesions, then 50% of 17 is 8.5, rounding up to nine (9) lesions; this means that the right side can have as few as eight lesions (17 minus 9). Subjects must have a minimum of eight lesions on each side.

The entire face, vertically from the hairline to mandible rim and horizontally from ear to ear (not including any lesions on or in the ear), including the nose, will be examined. Lesions will be counted separately for the right and left side of the subject's face. Lesions are defined as follows:

Non-inflammatory lesions:

- Comedones: open (blackheads) and closed (whiteheads).

Inflammatory lesions:

- Papules: raised inflammatory lesions with no visible purulent material.
- Pustules: raised inflammatory lesions with visible purulent material.

Nodulocystic lesions:

- Nodules and cysts: any circumscribed, inflammatory masses greater or equal to 5 mm in diameter with or without cystic changes.

## 10.3 VISIA Photography

Digital photographs will be taken of the face with the VISIA (Canfield Scientific) to document the progress of the subject (right vs left sides) in the study at Visit 1/Baseline, Visit 3, Visit 4, and Visit 5/EOT. At the election of the Sponsor, they may choose to perform an independent separate analysis of the photographs for clinical changes relative to Baseline.

The investigator may also elect to photograph the subject to document AEs or other findings at any time during the study as they deem appropriate.

## 10.4 Bioinstrumentation Assessments

TEWL and sebum measurements will be conducted on the right and left side of the face. Guidance regarding these measurements will be provided based upon additional details provided in a separate TEWL and Sebum Measurement Manual.

## 10.5 Safety Evaluations

### *10.5.1 Adverse Events*

All reported or observed AEs will be recorded. At each visit, subjects will also be questioned specifically about the status of any ongoing AEs. Untoward events that occur prior to the first dose of test article will be captured in the Medical History section of the CRF unless they are related to a study-specific procedure. AEs in the face will be segmented to the right and/or left sides of the face. See Section 14 for details on Adverse Event Reporting.

### *10.5.2 Local Skin Reactions*

At each visit, LSRs (erythema, edema, scaling/dryness, burning/stinging, pruritus, erosion, and pain) will be assessed. Erythema, edema, scaling/dryness, and erosion will be assessed by the investigator and burning/stinging, pain, and pruritus will be assessed by the subject. Assessments will be made using a 4-point ordinal scale where 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). Only LSRs that require medical intervention (e.g., prescription medication), require withholding or discontinuation of the application of the test article, or extend 2 cm beyond the Treatment Area will be documented as AEs. LSRs will be segmented to the right and/or left sides of the face. Any LSR that are not listed above will be recorded as an AE.

### *10.5.3 Urine Pregnancy Tests*

A UPT will be performed at Visit 1/Baseline and at Visit 5/Week 6/EOT for WOCBP.

### *10.5.4 Concomitant Medications and Concurrent Procedures/Therapies*

Concomitant medications and concurrent procedures/therapies will be reviewed at all visits and any changes will be recorded.

## 11. PHOTOGRAPHY

Photography documentation is required in this study so to participate in the study subjects must consent to photographs. Photographs taken as part of this study will be used to document the subject's baseline disease, AEs, or other findings during the study. The site will be provided with suggested guidelines to assist them in taking standardized photographs using the VISIA Camera system at Baseline. All photographs taken as part of this study are for informational purposes only and are not to assist in grading or for any other assessment. Photographs will be compiled and reviewed and may be used to evaluate investigator/grader training needs, but no formal assessments will be performed. However, the Sponsor reserves the right to have these photos evaluated using a separate independent grader evaluation at its discretion.

Note: Subjects who decline to have photographs taken during the conduct of study may continue to participate in the study. If a subject initially consents to photographs, then declines further photography as/if required, the Sponsor may use the photographs taken under consent for the purposes noted above.

Additional details regarding photographic methods, uploading and labeling photos, etc. will be provided in a Photo Manual to the site.

Photographic equipment will be provided by the Sponsor/Contract Research Organization (CRO) or the site may use its own photographic equipment if approved by the Sponsor or CRO.

## 12. LABORATORY TESTS

### 12.1 Urine Pregnancy Tests

The UPTs will be performed at the study site, if the site is registered and conforms to CLIA regulations for such testing (possesses a current valid CLIA Certificate of Waiver), or at an appropriately registered reference laboratory. The investigator will report the UPT results on the CRFs, in the subject's medical records, and in independent records maintained at the study site. The UPT used must have a minimum sensitivity of 25 mIU of β-hCG/mL.

# 13. END OF STUDY CRITERIA

At the end of each subject's participation in the study, the investigator will complete an End of Study form for all completed and discontinued subjects.

## 13.1 Completion of the Study

Subjects who complete the 6-week course of treatment and EOS visit as specified in this protocol will be considered to have completed the study.

## 13.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

- AEs
- Death
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject; NOTE: if the subject decides to withdraw from the study due to an AE then it should be classified as withdrawal due to an AE
- Other (e.g., any reason that may affect the outcome of the study or safety of subjects)

If a subject withdraws from the study prematurely for any reason, the site should make every effort to have the subject return to the clinic to perform all of the required visit activities and to collect and reconcile all test articles (if applicable). If the subject will not return to the clinic, the site should make every attempt to contact the subject; otherwise the subject will be considered lost to follow-up.

When a subject is withdrawn from the study for a test article related AE (as defined in Section 14.2), when possible, the subject should be followed until resolution or stabilization of the AE. If the subject is discontinued from the study due to pregnancy, the pregnancy and its outcome should be followed.

Subjects who are prematurely withdrawn or discontinued from the study will not be replaced.

### 13.3 Study Termination

The study may be terminated by the investigator or the Sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, he or she may stop the study. A study termination by the investigator will be reported to the Sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the Sponsor by the investigator within five working days.

In the event that the Sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

## 14. ADVERSE EVENT REPORTING

### 14.1 Adverse Event Definitions

An **adverse event** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with any drug) and from any route of administration, formulation, or dose, including an overdose.

A **suspected adverse reaction** is any AE for which there is a reasonable possibility that the drug caused the event. “Reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. For the purposes of prescription drug labeling, the term adverse reaction means an undesirable effect, reasonably associated with the use of a drug that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, the event is considered “unexpected” if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis

would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Timely and complete reporting of all AEs assists the Sponsor and/or their designee (e.g., Therapeutics, Inc. [TI]) in identifying any untoward medical occurrence, thereby allowing:

1) protection of the safety of study subjects;
2) a greater understanding of the overall safety profile of the test article;
3) recognition of dose-related test article toxicity;
4) appropriate modification of study protocols;
5) improvements in study design or procedures; and
6) adherence to worldwide regulatory requirements.

### 14.2 Adverse Event Details

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. All AEs must be recorded on the AE CRF. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of test article or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. AEs should be followed to resolution or stabilization (if possible) and, if they become serious, reported as SAEs (see Section 14.3). If possible, the outcome of any AEs that caused permanent discontinuation or that were present at the end of the study, especially those considered by the investigator to be related to the test article, should be reported.

Information on the medical condition of subjects should begin following the subject's written informed consent/assent (if applicable) to participate in the study and a medical history should be taken at screening. During any wash out and baseline periods, any changes in the health of subjects should be recorded as changes in medical history unless an event occurred as a result of a study-related procedure and is unanticipated; in such cases, the event should be recorded as an AE and reported to the Institutional Review Board (IRB) as an "unanticipated problem" in accordance with local procedures. Other changes in subject health information becomes AE data when the subject begins dosing with the test article; therefore AE data should be collected from the date of the first dose of test article until the date of the final study visit. These data are considered TEAEs.

The investigator will instruct the subject to report any AEs that may occur during the study. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject's overall health status since the previous visit.

The severity of each AE, as judged by the investigator, will be recorded on the appropriate AE CRF and will be graded according to the following scale:

**Mild** - The AE is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

**Moderate** - The AE is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

**Severe** - The AE interrupts usual activities of daily living or significantly affects clinical status, or may require intensive therapeutic intervention.

The investigator must determine the relationship of the AE to the test article according to the following categories:

**Definitely Related** - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage, and reappearance of the event on repeated exposure (re-challenge).

**Probably Related** - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage of the test article; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.

**Possibly Related** - An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; but may have been caused by concurrent/underlying illness, other drug, procedure, or other causes.

**Unlikely Related** - An event that does not follow a reasonable temporal sequence from administration of the test article; that does not follow a known or expected response pattern to the test article, or most likely was caused by concurrent/underlying illness, other drug, procedure, or other causes, because of their known effects.

**Not Related** - An event almost certainly caused by concurrent/underlying illness, other drug, procedure, or other causes.

The investigator should categorize the outcome of the AE according to the following categories:

**Fatal** - Termination of life as a result of an AE.

**Not Recovered/Not Resolved** - AE has not improved or the subject has not recuperated.

**Recovered/Resolved** - AE has improved or the subject has recuperated.

**Recovered/Resolved with Sequelae** - subject recuperated but retained the pathological conditions resulting from the prior disease or injury.

**Recovering/Resolving** - AE is improving or the subject is recuperating.

**Unknown** - Not known, not observed, not recorded or subject refused.

### 14.3 Serious Adverse Event

An event that is serious must be recorded on the AE CRF and on the TI SAE Report Form, and requires expeditious handling to comply with regulatory requirements.

An AE or suspected adverse reaction is considered "serious" if, in the opinion of either the investigator or Sponsor, it results in any of the following outcomes:

- Death; the event must be the cause of death for the SAE to meet this serious criterion.
- Life-threatening event; an event in which the subject was at risk of death at the time of the event and not an event that hypothetically might have caused death if it had been more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization (for ≥24 hours).
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical events; a medical event(s) that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events NOT considered to be SAEs are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen; and
- Treatment on an emergency, outpatient basis, for an event not fulfilling any of the definitions of "serious" given above and not resulting in hospital admission.

AEs classified as "serious" by either the investigator or the Sponsor require expeditious handling and reporting to TI to comply with regulatory requirements. **All SAEs, whether related or unrelated to test article, must be immediately reported by telephone to the Medical Monitor and, in the event that he/she is unavailable, to the Project Manager listed on the first page of the protocol.** Written notification of all SAEs should be sent to the Project Manager by email or confirmed facsimile transmission. These include those SAEs listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the test article caused the event.

Any suspected adverse reactions that are serious and unexpected represent especially important safety information that must be reported more rapidly to Health Authorities; therefore, it is important that the Investigator submit any information requested by the Sponsor or designee (e.g., TI) as soon as it becomes available.

If only limited information is initially available, follow-up reports are required. Should the investigator become aware of an SAE (regardless of its relationship to test article) that occurs within 30 days after stopping the test article, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to TI, if available.

As required, the Sponsor or designee (e.g., TI) will notify participating investigators of all suspected adverse reactions that are serious and unexpected. This notification will be in the form of an IND safety report of potential serious risks as soon as possible but no later than 15 calendar days after the Sponsor determines that the information is "reportable" according to the criteria listed in 21 CFR Section 312.32. These are:

i) Serious and unexpected suspected adverse reactions;
ii) Findings from other studies including epidemiological studies, pooled analyses, or other clinical studies that suggest a significant risk in humans exposed to the test articles;
iii) Findings from animal or in vitro tests that suggest a significant risk to humans exposed to the test articles, or reports of significant organ toxicity at or near the expected human exposure; and
iv) Clinically important increases in the rate of occurrence of serious suspected adverse reactions.

Upon receiving such notices, the investigator must review and retain the notice with the IB and promptly submit a copy of this information to the responsible IRB according to local

regulations. The investigator and IRB will determine if the informed consent/assent (if applicable) requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of safety updates by the investigator to Health Authorities should be handled according to local regulations.

The Sponsor or designee may be required to report certain SAEs to regulatory authorities (e.g., United States FDA) within seven calendar days of being notified about the event; therefore, it is important that investigators submit any information requested by the Sponsor or designee as soon as it becomes available.

### 14.4 Laboratory Test Abnormalities

There are no specific laboratory tests, other than a UPT, required in this study.

### 14.5 Pregnancy

WOCBP (see Schedule of Events for definition of WOCBP) must have a UPT prior to study enrollment. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during the study and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent/assent (if applicable) form documenting this discussion.

WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If a subject or investigator suspects that a subject may be pregnant at any time during the study, the test article must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or apply further test article and must be discontinued from the study unless the Sponsor or the Medical Monitor elects to keep the subject in the study for safety follow-up purposes.

If following initiation of study treatment, it is subsequently discovered that a subject was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the Medical Monitor of this event and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to TI. The investigator must notify the IRB of any pregnancy associated with the study treatment and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated, including counseling of the subject by the investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the investigator must report to TI, on the appropriate pregnancy surveillance form(s), any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs or SAEs

(if they fulfill the SAE criteria). Offspring should be followed for a minimum of eight weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to the test article(s) should be recorded as a SAE with details documented in the pregnancy surveillance form. Abortion, whether accidental, therapeutic, or spontaneous should be reported as an SAE.

## 15. BLINDING/UNBLINDING

An Unblinded Evaluator will document AEs and LSRs. A Blinded Evaluator will perform clinical evaluations (IGA and lesion counts). The Blinded Evaluator will not be involved in randomization, test article application instructions, or documentation of test article compliance.

## 16. CLINICAL SUPPLIES

### 16.1 Test Article Information

Test articles will be packaged and labeled by the Sponsor or designee. Detailed information on the packaging/labeling, blinding/unblinding, storage and preparation, dispensing, accountability, etc. is included in Appendix 3.

### 16.2 Supplies Provided by Therapeutics, Inc.

- CRFs
- Source document draft templates
- Site regulatory binder
- UPT kits
- Standard facial cleanser

### 16.3 Supplies Provided by Investigator

- Personal computer to store and view study images
- Urine collection containers for UPTs

### 16.4 Supplies Provided by Foamix Pharmaceuticals

- Samples for demonstration to subjects of test article application

## 17. STATISTICAL CONSIDERATIONS

### 17.1 Sample Size

This is a pilot proof of principle study, as such no specific power calculations were used to establish the sizing of this study.

## 17.2 Endpoints

### *17.2.1 Efficacy Endpoints*

- IGA Assessment
    - IGA within subject, Treatment A versus Treatment B – at Week 6; Treatment A> Treatment B, Treatment A= Treatment B, Treatment A< Treatment B
    - IGA scores will be dichotomized to "success" or "failure" where "success" is defined as at least a two-point improvement in IGA score relative to Baseline, Treatment A versus Treatment B
- Absolute and Percent Change from Baseline to Week 6 in the inflammatory (papules and pustules) lesion count, within subject Treatment A vs Treatment B
- Absolute and Percent Change from Baseline to Week 6 in the non-inflammatory (open and closed comedones) lesion count, within subject Treatment A vs Treatment B
- Sebum and TEWL assessments relative to Baseline versus Weeks 2, 4, 6, and 7, within subject Treatment A versus Treatment B
- VISIA Digital Photographs may undergo an independent separate analysis for clinical changes relative to Baseline.

### *17.2.2 Safety Endpoints*

Safety endpoints will include:

- Incidence (severity and causality) of any reported or observed TEAEs, whether or not they are considered to be related to the test article. Note: all application site AEs will be analyzed for Test Article A vs Test Article B involvement.
- Number of subjects with improved/same versus worsened severities compared to Baseline of the following LSRs: erythema, edema, scaling/dryness, burning/stinging, pruritus, erosion, and pain at each time point, Test Article A vs Test Article B.

## 17.3 Statistical Methods

All statistical processing will be performed using SAS® Version 9.4 unless otherwise stated.

The Safety population will include all randomized subjects who received test article and applied at least one application.

The modified intent-to-treat (mITT) population will include all randomized subjects who met all I/E criteria, applied at least one dose of test article, and returned for at least one post-Baseline evaluation visit.

The per-protocol (PP) population will include all randomized subjects who met all mITT population criteria, were compliant with the assigned test articles based on the subject diaries (applied at least CCI and no more than CCI of the expected test article applications for the specified duration of the study), did not miss the scheduled test article applications for more than three consecutive days (i.e., three consecutive days with no test article application), have no other evidence of material dosing noncompliance, and completed the primary endpoint evaluation at Week 6 within the designated visit window (±3 days) with no protocol violations and prohibited medications that would affect the treatment evaluation.

### *17.3.1 Dosing Compliance*

As appropriate, outcomes relative to Test Article A vs Test Article B shall be tabulated. Descriptive statistics will be used to summarize test article compliance for each analysis population. Compliant subjects are defined as those who apply at least CCI and no more than CCI of the expected test article applications (Right and Left face), and did not miss scheduled applications for more than three consecutive days. The percentage of compliant subjects will also be presented.

### *17.3.2 Efficacy Analyses*

As appropriate, outcomes relative to Test Article A vs Test Article B will be tabulated for all visits. The efficacy analyses will be conducted on the mITT and PP populations and will be compiled using descriptive statistics only for all efficacy variables.

### *17.3.3 Safety Analyses*

As appropriate, outcomes relative to Test Article A vs Test Article B will be tabulated. All safety analyses will be performed in the Safety population unless otherwise stated.

#### 17.3.3.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percent of unique subjects reporting each TEAE will be summarized by MedDRA system organ class (SOC), MedDRA preferred term (PT), and treatment group. AEs will also be similarly summarized by SOC, PT, maximum severity, and treatment group as well as by SOC, PT, and closest relationship to test article. Application site AEs will be summarized separately by treatment group. All AEs reported during the study will be listed.

#### 17.3.3.2 Local Skin Reactions

The frequency of the individual LSRs (erythema, edema, scaling/dryness, burning/stinging, pruritus, erosion, and pain) will be tabulated by severity and treatment group at each onsite clinic visit. Subject counts for improved/same versus worsened compared to Baseline value will be also presented for the post-baseline visits.

### 17.4 Subgroup Analyses

There are no subgroup analyses planned for this study.

### 17.5 Interim Analyses

There are no interim analyses planned for this study.

## 18. ETHICAL AND REGULATORY CONSIDERATIONS

### 18.1 Compliance with Good Clinical Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice guidelines and with other applicable regulations. The investigator and all study staff will conduct the study in compliance with this protocol. The protocol, informed consent/assent (if applicable) documents, recruitment advertisements, and any amendments to these items will have IRB approval prior to study initiation. Voluntary informed consent/assent (if applicable) will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their assigned responsibilities. Contact information for each site and any clinical laboratories used in the study will be maintained up to date in a separate reference document.

### 18.2 Institutional Review Board and Informed Consent

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent/assent (if applicable) form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to the subject/and parent/guardian or care giver (if applicable). The investigator should also provide the IRB with a copy of the product labeling, information to be provided to the subject and parent/guardian or care giver (if applicable) and any updates. The investigator will submit documentation of the IRB approval to TI.

The IRB approved consent/assent (if applicable) form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The investigator/designee will explain the study to each potential subject and parent/guardian (if applicable) and the subject must indicate voluntary consent/assent by signing and dating the approved informed consent/assent (if applicable) form. The parent or legal guardian must provide written informed consent for the subject. The investigator must provide the subject and parent/guardian (if applicable) with a copy of the consent/assent (if applicable) form, in a language the subject understands.

The investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

### 18.3 Protocol Compliance

The IRB approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

### 18.4 Protocol Revisions

TI must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding this study must be sent to TI.

New or altered consent/assent (if applicable) forms required by the IRB due to a protocol change must be signed by all subjects/care givers (if applicable) currently enrolled in the study and must be used for any subsequent subject enrollment.

### 18.5 Study Monitoring

Representatives of TI and/or the Sponsor must be allowed to visit all study sites, to review study records, and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff, and to verify that the investigator, study staff, and facilities remain acceptable for the conduct of the study.

Representatives of government regulatory authorities may also evaluate the study records, source documents, investigator, study staff, and facilities.

The investigator should immediately notify TI of any audits of this study by any regulatory agency and must promptly provide copies of any audit reports.

### 18.6 Case Report Form Requirements

This study utilizes paper CRFs; all forms must be completed legibly in black ink. All requested information must be entered on the CRFs in the areas provided. All corrections should be made by striking through the incorrect entry with a single line then entering the correct information adjacent to the incorrect entry. Every correction must be initialed and dated by the individual making the correction on the date the correction was made. Only individuals listed on the Delegation of Responsibilities Log with responsibility for CRF completion may make entries on the CRFs.

The investigator or physician sub-investigator must review, sign, and date the subject's CRFs as specified in the case books.

### 18.7 Reports to Institutional Review Board

The investigator should provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements or Institution procedures.

### 18.8 Quality Assurance Audits

Representatives from TI and/or the Sponsor or a third party selected by the Sponsor may conduct a quality assurance audit of this study. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authorities, the investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The investigator must notify TI in the event of a FDA site audit.

### 18.9 Records Retention

The investigator must maintain all study records (including test article disposition, informed consents/assents, CRFs, source documents, correspondence, regulatory documents, contracts, etc.) for the maximum period required by TI or the institution where the study is conducted, whichever is longer. Test Article Accountability Logs and original Label Pages (if applicable) must be kept with study records at the site.

The investigator must contact TI or the Sponsor prior to destroying any records associated with this study.

If the investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to TI.

### 18.10 Record Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject or the subject's parent/guardian (if appropriate), except as necessary for monitoring by TI or the Sponsor, the FDA or other regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study shall not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from TI or the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

## 19. REFERENCES

1. Brown SK, Shalita AR. Acne vulgaris, folliculitis, and acne rosacea. Lancet. 1998;351:1871-1876.

## APPENDIX 1 SAMPLE SUBJECT INSTRUCTION SHEET

Copies of the following sample subject instructions will be provided to the study site. The investigator must give each subject/parent/guardian/care giver (if applicable) a copy of this instruction sheet at Visit 1/Baseline.

**SAMPLE SUBJECT INSTRUCTION SHEET**

Please read and follow these instructions carefully. Contact the study staff at the telephone number noted below if you have any questions about the study:

Contact:_____ At:_____

Please apply the study products to the correct sides of your face **ONCE DAILY in the evening every day for 6 weeks.**

**STUDY PRODUCT APPLICATION INSTRUCTIONS:**

One study product is provided in a canister and one study product is provided in a squeeze bottle. The study products are color-coded and labeled according to which side you should dose; you must not mix up the containers and apply the wrong study product to the wrong side of your face.

CCI [redacted]

**Before applying the study product please confirm you are using the correct color coded study product for the side of the face you are treating.**

Wash your entire face with the provided facial cleanser and water and gently pat dry.
Wash and dry your hands before and after both study product applications.

**WHEN USING THE STUDY PRODUCT CANISTER:** Shake the study product canister well before use. To dispense the study product, hold the canister in the upright position and press down on the actuator (see diagram to the right).

a) Dispense about ¼ gram (or a half of a cherry size) of the study product onto the fingertip of the hand.
b) Gently dab small amounts of the study product over the correct side of your face, then spread the product evenly with your fingertip to COVER ALL FACIAL SKIN ON THE CORRECT SIDE OF YOUR FACE FROM THE HAIRLINE TO THE JAWLINE AND AVOID CROSSING THE MIDLINE with a thin, uniform layer until the study product is absorbed.
c) Record the date and time of study product application in your Subject Diary.
d) Wash your hands.

**WHEN USING THE STUDY PRODUCT SQUEEZE BOTTLE:** Flip open the cap and uniformly wet an application pad with the study product. If necessary re-wet the pad one more time if additional product is needed to cover the entire half of the face. Close the flip cap when done.

a) Using the moistened pad, gently apply a uniform coat of the solution on the correct side of the face. BEGIN ON THE FOREHEAD USING GENTLE STROKES STARTING AT THE MIDLINE MOVING TOWARDS THE CORRECT SIDE OF THE FACE WORKING DOWNWARD TO THE CHIN. COVER ALL FACIAL SKIN ON THAT SIDE OF THE FACE FROM THE HAIRLINE TO THE JAWLINE AND AVOID CROSSING THE MIDLINE.
b) Record the date and time of study product application in your Subject Diary.
c) Wash your hands.

**REMINDERS:**

- **The study products should be applied at approximately the same time each day, preferably about 1 hour before bedtime.**
- **Do not wash face or apply the study products and allowed skin care products within 4 hours before any study visit.**
- **After study product applications, allow a 1 hour dry-down period before applying any other approved facial product.**
- Do not wash the treated area for at least 4 hours after study product applications.
- Store the study products according to the instructions on the label.
- If you miss a dose, apply the next dose at the regular time.
- Bring all containers of the study products (used and unused) and the completed Subject Diary to each visit.
- Do not allow anyone else to use the study products.
- Keep containers of study products away from children/pets.
- Only apply the study products as directed by the study doctor.
- Do not apply the study products to any area other than your face.
- If skin irritation develops, discontinue use and contact the study site immediately.
- Avoid contact with eyes and all mucous membranes. If contact with eyes occurs, rinse thoroughly with cool tap water.

**STUDY VISIT SCHEDULE:**

| Visit 2 | Visit 3 | Visit 4 | Visit 5 |
|---|---|---|---|
| Date:<br>Time: | Date:<br>Time: | Date:<br>Time: | Date:<br>Time: |

## APPENDIX 2 SAMPLE SUBJECT DIARY

A copy of the following sample Subject Diary will be provided to the study site. The investigator must give each subject/parent/guardian/care giver (if applicable) a copy of this Subject Diary at Visit 1/Baseline and all follow-up visits, as necessary.

| PROTOCOL: | SITE: | SUBJECT NO.: | INITIALS: |
|---|---|---|---|
| FX2018-23 | _____ _____ | _____ _____ _____ | _____ _____ _____ |

**SAMPLE SUBJECT DIARY**

Apply the study products as prescribed. Contact the study staff at the telephone number below if you have any questions about the study.

Contact:_____ At:_____

After dosing, record the date and time of the study product applications.
If you miss a dose, write *MISSED* in the space for time.

| DATE (dd/Mmm/yyyy) | DOSE (Time) | | DATE (dd/Mmm/yyyy) | DOSE (Time) | | DATE (dd/Mmm/yyyy) | DOSE (Time) | |
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**Next Appointment: _____/_____/_____at_____AM/PM**
**Weekday dd MMM yyyy**

| *Site Use Only:* | **Diary Dispensed at:** ☐ **Visit 1 (Day 1)** ☐ **Visit 2 (Week 1)** ☐ **Visit 3 (Week 2)** ☐ **Visit 4 (Week 4)** | **Date Dispensed:** | **Date Returned:** |
|---|---|---|---|

# APPENDIX 3 TEST ARTICLE INFORMATION

## A 3.1 Test Article Packaging and Labeling

The test articles will be packaged and labeled by the Sponsor or designee. FMX101 vehicle will be packaged in a canister and the hydro-alcohol solution based vehicle will be packaged in a squeeze bottle. Each subject will be assigned a subject number and provided with sufficient test article in standard packaging for the designated treatment period during the study.

Each container of the test article will contain, at a minimum, the following information: the protocol number, subject identifiers (e.g., subject number and initials), the contents, the container number, an investigational test article disclaimer (e.g., Caution: New Drug Limited by United States law to investigational use), and the appropriate storage conditions for the test article.

The randomization will be blocked by investigational site. When test article containers are dispensed to the subjects, the Subject label must be completed entirely with the necessary information and recorded in the Test Article Accountability Log at the investigational site.

## A 3.2 Test Article Storage and Preparation

FMX101 vehicle canisters must be stored at 2°C – 8°C until being dispensed to the subject. Subsequently, they must be stored at 20°C – 25°C (refer to USP Controlled Room Temperature).

Hydro-alcohol solution based vehicle squeeze bottles must be stored at 20°C – 25°C both at the study site and after being dispensed to the subject.

The investigator will be responsible for the suitable storage of the investigational products in compliance with the storage instructions and must restrict access to the study personnel only.

## A 3.3 Dispensing Test Article

Sites will receive shipments of one or more blocks of test articles. Subjects who are eligible for enrollment into the study will be assigned a three-digit subject number by the study staff in ascending order beginning with the lowest available number.

The test article must be dispensed only to study subjects and only at study sites specified on the form FDA 1572 by authorized personnel as required by applicable regulations and guidelines.

On dispensing the test article for the first time at Visit 1/Baseline, the weight of the containers will be measured prior to dispensing. Sufficient test article for the designated

treatment period will be dispensed to the subject and the information recorded on the Test Article Accountability Log. The subjects will be instructed to bring all containers of the test article (used and unused) to each clinic visit.

At each post-Baseline visit, site staff will collect all containers (used and unused) of the test article, weigh the returned test articles, and record the necessary information in the Test Article Accountability Log. Site staff will review the test article application procedure and subjects will be counseled on test article compliance, as necessary. Any discrepancies or concerns with the subject regarding the use of the Subject Diary to record test article applications should be addressed. Additional containers of the test article will be dispensed to the subject, as needed, to ensure that each subject has sufficient test article for the designated treatment period.

### A 3.4 Test Article Supply Records at Study Sites

It is the responsibility of the investigator to ensure that a current record of test article disposition is maintained. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of the person responsible for each product inventory entry/movement.
- Amount (number and units and weights) dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor.
- Amount destroyed at study site, if applicable.

TI will provide forms to facilitate inventory control if the staff at the study site does not have an established system that meets these requirements.

### A 3.5 Dose Modifications

The subject should not modify the treatment regimen without consultation with the investigator. Subjects should be instructed to discontinue use if significant skin irritation or rash develops and to contact the study site. In the event that the investigator believes that dose modification is necessary (e.g., problems with tolerance), the subject's care should be discussed with the Medical Monitor prior to making any dose modifications. All dose modifications must be reported on the appropriate CRF.

### A 3.6 Documentation of Application and Compliance

The date of the first and last application of the test article will be recorded on the appropriate CRF. A CRF will also be used to record any changes from the application specified in the protocol (e.g., missed applications, investigator directed reduction in application frequency, etc.).

A Subject Diary will be dispensed to subjects to record the dates and times of all applications and to record any missed doses of the test article (Appendix 2). Subjects will be instructed to bring the Subject Diary with them to each study visit.

### A 3.7 Return and Destruction of Test Article Supplies

Upon completion or termination of the study, all remaining test article containers must be a) returned to TI, Sponsor, or designee by a traceable method for final accountability and destruction or b) appropriately destroyed in accordance with applicable regulations with the provision of a certificate of destruction. All missing containers of test article must be explained on the completed Test Article Accountability Log. A copy of the Test Article Accountability Log and original Label Pages (if applicable) will be returned to TI or designee.

## APPENDIX 4 PROTOCOL AMENDMENTS

### PROTOCOL AMENDMENT #1
**Date of Amendment: November 13, 2018**

This protocol was amended as follows:

- The efficacy endpoint for the VISIA assessment was fixed to be optional, which aligns with the language used in other parts of the protocol that describe the VISIA assessment.
- The ingredients in Test Article B were updated.
- Text was updated to reflect that the test articles will not be dispensed in kits.
- Subject numbers were updated to be three digit numbers.
- The age range was changed from 12-40 years of age (inclusive) to 9 years of age or older.
- The assessment of LSRs was changed from being done by a Blinded Evaluator to being done by an Unblinded Evaluator (i.e., the investigator).

Specific changes to the protocol are listed below; new or revised sections are included (Added text has been **bolded** and deleted text has been ~~redlined~~). Minor typographical errors, grammatical, and wording changes are not included in this section.

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| **Study Endpoints (Synopsis, Section 17.2.1)** | • VISIA Digital Photographs ~~will~~ **may undergo an independent separate** ~~be~~ analy**sis**~~zed~~ for ~~Absolute and Percent Change from Baseline to Week 6 for lesion counts, erythema, hyper-pigmentation, and skin texture, within subject Test Article A vs Test Article B~~**clinical changes relative to Baseline**. |
| **Study Population (Synopsis)** | Healthy male or female subjects ~~12 to 40 years of age (inclusive)~~**9 years of age or older** with a clinical diagnosis of symmetric moderate facial acne vulgaris (Grade 3 on the Investigator's Global Assessment [IGA]), ≥16 inflammatory lesions (i.e., papules and pustules) on the face, and no more than two active nodules on the face. |
| **Inclusion Criteria (Synopsis, Section 5.1.1)** | Subject is a healthy male or non-pregnant, non-breastfeeding female ~~12 to 40~~ **9** years of age **or older** ~~(inclusive)~~ at the time of consent/assent. |
| **Study Procedures (Synopsis)** | NOTE: Clinical evaluations (Right and Left Facial IGA and lesion counts) ~~and local skin reaction (LSR) assessments~~ will be performed by a Blinded Evaluator who is not involved in |

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| | randomization, test article application instructions, or documentation of test article compliance.<br><br>LSRs will be assessed ~~by a Blinded Evaluator~~ 15 minutes following test article application.<br><br>LSRs will be assessed ~~by a Blinded Evaluator~~ for the Right and Left side of the face.<br><br>The subject will return to the clinic for review of concomitant medications and procedures/therapies, LSRs~~ (by a Blinded Evaluator),~~ and AEs. |
| **Study Measurements (Synopsis)** | At each visit, LSRs (erythema, edema, scaling/dryness, burning/stinging, pruritus, erosion, and pain) will be assessed ~~by a Blinded Evaluator.~~ |
| **Section 4** | This is a randomized, evaluator-blinded, bilateral comparison study of FMX101 hydrophobic oil based vehicle (Test Article A) and hydro-alcohol solution based vehicle (Test Article B) in healthy male or female subjects ~~12 to 40 years of age~~**9 years of age or older** with facial acne vulgaris. |
| **Section 6.1** | water, alcohol denatured, butylene glycol, **poloxamer 124, lactic acid,** PEG-40 hydrogenated castor oil, **sodium hydroxide,** ~~poloxamer 124, lactic acid,~~glyceryl caprylate, phenoxyethanol, ~~methylparaben,~~and fragrance. |
| **Section 9** | ~~Must be performed by a Blinded Evaluator:~~ Assess LSRs on the Right and Left sides of the face separately prior to first test article applications. |
| **Section 10** | Clinical evaluations (Right and Left Facial IGA and lesion counts) ~~and LSR assessments~~ will be performed by a Blinded Evaluator who is not involved in randomization, test article application instructions, or documentation of test article compliance. The same Blinded Evaluator should evaluate a subject over the course of the study. The study staff, the Unblinded Evaluator, and subjects will also be instructed not to discuss the treatment, AEs, SAEs, or any study experiences with the Blinded Evaluator. |

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| | The Blinded Evaluator will only have access to the page in the CRF required to document the Right and Left Facial IGA and lesion counts~~ and LSR assessments~~; all other CRF content will be inaccessible. |
| **Section 10.5.2** | At each visit, LSRs (erythema, edema, scaling/dryness, burning/stinging, pruritus, erosion, and pain) will be assessed~~ by a Blinded Evaluator~~. Erythema, edema, scaling/dryness, and erosion will be assessed by the ~~Blinded Evaluator~~**investigator** and burning/stinging, pain, and pruritus will be assessed by the subject. |
| **Section 15** | An Unblinded Evaluator will document AEs **and LSRs**. A Blinded Evaluator will ~~assess LSRs and~~ perform clinical evaluations (IGA and lesion counts). |
| **Appendix 3 Section 3.1** | ~~Containers of the test article will be contained in subject kits.~~ The randomization will be blocked by investigational site. When ~~kits~~**test article containers** are dispensed to the subjects, the Subject ~~Kit~~ label must be completed entirely with the necessary information and recorded in the Test Article Accountability Log at the investigational site. ~~In the event of an emergency, the contents of the kit test article containers can be unblinded using the proper procedures as outlined in the protocol and by instructions provided to the site.~~ |
| **Appendix 3 Section 3.3** | Subjects who are eligible for enrollment into the study will be assigned a ~~two~~**three**-digit subject number by the study staff in ascending order beginning with the lowest available number. |