A Randomized, Double-Blind Study to Compare the Efficacy, Safety and Long-Term Safety of Topical Administration of FMX-101 for 1 Year in the Treatment of Moderate-to-Severe Acne Vulgaris, Study FX2014-05

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16.1.1 Protocol and Amendments

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Protocol version 3, 06 April 2016

CLINICAL STUDY PROTOCOL

Title:	A Randomized, Double-Blind Study to Compare the Efficacy, Safety and Long-Term Safety of Topical Administration of FMX-101 for 1 Year in the Treatment of Moderate-to-Severe Acne Vulgaris, Study FX2014-05
Development Phase:	3
Project Number:	FMX-101
Study drug(s):	FMX-101, minocycline foam 4%; matching vehicle foam
Indication:	Acne vulgaris
Authors:	PPD
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Title: A Randomized, Double-Blind Study to Compare the Efficacy, Safety and Long-Term Safety of Topical Administration of FMX-101 for 1 Year in the Treatment of Moderate-to-Severe Acne Vulgaris, Study FX2014-05

CONFIDENTIAL

PROJECT NUMBER: FMX-101

	Name/Title	Signature	Date
CLINICAL RESEARCH:	PPD PPD	PPD	10/14/16
REGULATORY AFFAIRS:	PPD PPD	PPD	10/14/16

1. SYNOPSIS

This is a Phase 3 study to evaluate the efficacy, safety and long-term safety of the topical administration of FMX-101, 4% minocycline foam for the treatment of moderate-to-severe acne vulgaris. The first 12 weeks of the study involves randomized, double-blind treatment with active FMX-101, 4% or matching vehicle. Subjects who successfully complete the 12-week double blind portion of the study may be offered the opportunity to continue in the trial for up to an additional 40 weeks (for a total of 1 year) and receive open-label treatment with FMX-101, 4%.

1.1. Investigational Product, Dosage, and Mode of Administration

The investigational product is FMX-101, minocycline foam 4%. FMX-101 4% will be applied topically daily for the 12-week treatment duration of the study.

1.2. Active Ingredient

The active ingredient is minocycline HCl.

1.3. Reference Product, Dosage, and Mode of Administration

The reference product is vehicle foam. Vehicle foam will be applied topically daily for the 12-week treatment duration of the study.

1.4. Study Centers

Approximately 30 study centers will participate in this study.

1.5. Study Period

Estimated date first subject enrolled: April 2016

Estimated date last subject completed: August 2017

1.6. Study Objectives

The objectives of this study are:

- To evaluate the efficacy in the treatment of acne compared to vehicle of topical FMX-101, 4% administered daily for 12 weeks
- To evaluate the safety compared to vehicle of topical FMX-101, 4% administered daily for 12 weeks
- To evaluate the long-term safety of topical FMX-101, 4% administered daily for up to 40 additional weeks

1.7. Methodology

The study will have 2 parts. The first will involve 12 weeks of double-blind treatment with FMX-101, 4% or vehicle foam. The second will involve up to 40 additional weeks of open-label treatment with FMX-101, 4% of subjects who complete the first part of the study.

1.7.1. Part 1 – Double-blind Period

This is a randomized, multicenter, double-blind, vehicle-controlled, 2-arm study to evaluate the safety and efficacy over 12 weeks of FMX-101 minocycline foam, 4%, compared to vehicle, in the treatment of subjects with moderate to severe facial acne vulgaris.

Qualified subjects will be randomized to receive 1 of the following 2 treatments:

- FMX-101, 4% minocycline foam
- Vehicle foam

Subjects with qualifying lesion counts (Section 8.1.2) and Investigator's Global Assessments (IGA, Section 8.1.1) of acne severity scores and will be assigned to 1 of 2 treatments according to the randomization schedule. Subjects will apply the assigned study drug topically once daily for 12 weeks as directed. Subjects will be advised to apply the study drug at approximately the same time each day, preferably in the evening at bedtime. Both the Investigator and subject will be blinded to the study drug identity.

Subjects will return for visits at Weeks 1, 3, 6, 9, and 12. At the discretion of the clinic staff, for the convenience of subjects or clinic staff, visits can be scheduled to occur 3 days before or after the nominal schedule date for the Weeks 1, 3 and 6 visits and 7 days before or after for the Weeks 9 and 12 visits. Efficacy evaluations (acne lesion counts and IGAs will be performed at Weeks 3, 6, 9, and 12 during the study. Other assessments will be performed as described in Section 9.

1.7.2. Part 2 – Open-label

At the Week 12 Visit, subjects whose IGA score has not worsened may be invited to continue into the open-label part of this study for an additional 9 months of treatment. Subjects will be enrolled in this phase of the study until a total of approximately 400 subjects from Studies FX2014-04 and FX2014-05 have elected to continue in the open-label portion of their respective study. Subjects who elect to continue into the open-label part of this study will receive supplies of active FMX-101, 4% minocycline foam.

Treatment during this part of the study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment of some or all areas if there is clinical improvement or resolution of the acne in those areas. Even if the treatment is partially or completely temporarily suspended, the subject will be continued in the study and will make all scheduled clinic visits. If at any time the acne recurs or worsens, treatment of the affected areas may be resumed.

Subjects may be discontinued from the study after 12 weeks if their disease becomes refractory or they become intolerant of the product.

1.8. Number of Subjects

The planned enrollment is 450 subjects. Subjects will be randomized to active or vehicle in a 2:1 ratio. Approximately 300 and 150 subjects will be assigned to the FMX-101, 4% or vehicle treatment groups, respectively.

1.9. Diagnosis and Main Criteria for Inclusion

Subjects are to be at least 9 years of age.

Eligible subjects are to have a diagnosis of facial acne vulgaris characterized by (subjects are permitted to also have acne on other parts of the body):

- 20 to 50 inflammatory lesions (papules, pustules, and nodules)
- 25 to 100 noninflammatory lesions (open and closed comedones)
- No more than 2 nodules on the face
- Investigator's Global Assessment (IGA) score of moderate (3) to severe (4)

1.10. Criteria for Evaluation

1.10.1. Efficacy

The efficacy assessments will include the IGA and lesion counts at Baseline and Weeks 3, 6, 9 and 12.

1.10.2. Safety

The safety assessments in this study are physical examinations, vital signs, assessment of the skin at application site(s), adverse events (volunteered, observed, and elicited by general questioning in a non-suggestive manner), and clinical laboratory test results.

1.11. Statistical Methods

Efficacy analyses will be conducted on the Intent-to-Treat (ITT) population, using the last-observation-carried-forward (LOCF) approach to impute missing values. Supportive efficacy analyses will also be conducted on the Per Protocol (PP) population, with no imputation for missing values. The co-primary efficacy endpoints are the absolute change from Baseline in the inflammatory lesion count at Week 12 IGA Treatment Success (dichotomized as Yes/No) at Week 12, where success is defined as an IGA score of 0 or 1, and at least a 2-grade decrease from Baseline. FMX-101 4% will be tested against vehicle at the two-sided 0.05 level of significance without adjustment for multiplicity. The absolute change from Baseline in inflammatory lesions at Week 12 will be analyzed using an Analysis of Covariance (ANCOVA) model with main effect treatment and investigational site as a covariate. The IGA Treatment Success rates will be compared between the treatment groups using a Cochran–Mantel–Haenszel (CMH) test stratified for investigational site.

No statistical tests will be performed for any of the safety assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
CFR	Code of Federal Regulations
CRF	Case report form
eCRF	Electronic case report form
EKG	Electrocardiogram
FDA	Food & Drug Administration
GCP	Good Clinical Practice
HEENT	Head, eyes, ears, nose, and throat
ICF	Informed consent form
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
IWRS	Interactive Web Response System (IWRS)
LOCF	Last-observation-carried-forward
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OC	Observed-Cases
P. acnes	Propionibacterium acnes
PP	Per protocol
TEAE	Treatment-emergent adverse event
SAE	Serious adverse event
SOC	System organ class

STUDY ADMINISTRATIVE STRUCTURE

Name	Affiliation / Address / Telephone Number	Responsibility
Foamix Pharmaceuticals, Inc	520 U.S. Highway 22, Suite 305 Bridgewater, NJ 08807	Sponsor
TKL Research, Inc.	365 West Passaic Street, Suite 550 Rochelle Park, NJ 07662	CRO
PPD	TKL Research, Inc.	PPD
PPD	TKL Research, Inc.	PPD

2. INTRODUCTION

Acne vulgaris is a common disease of both males and females, usually manifesting initially during adolescence. The primary pathologic events are initiated in the pilo-sebaceous 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 pilo-sebaceous follicle and increased sebum produced in the gland, a blockage of the duct results in the inapparent clinical lesion of the microcomedone. Continued blockage, colonization of the follicle by Propionibacterium acnes (P. 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]

FMX-101, 4% is a minocycline containing topical foam being developed as a treatment for acne vulgaris. Antibiotics, especially erythromycin, minocycline, and doxycycline, have been prescribed as acne treatments for many years. These antibiotics effectively control the signs of inflammatory acne while patients continue to use them. Nonclinical studies have demonstrated that FMX-101, 4% exhibits favorable characteristics.

Foamix has conducted 2 Phase 1 and 1 Phase 2 study of FMX-101, 4% to assess its safety and tolerability. FMX-101, 4% has been shown to be effective and well tolerated at the 4% dose that is being utilized in this study. The Investigator's Brochure should be consulted for summaries of the results of these studies.

This Phase 3 study (Study FX2014-05) will assess the efficacy, safety and long-term safety of FMX-101, 4% for the treatment of moderate to severe facial acne vulgaris.

3. STUDY OBJECTIVES

The objectives of this study are:

- To evaluate the efficacy in the treatment of acne compared to vehicle of topical FMX-101, 4% administered daily for 12 weeks
- To evaluate the safety compared to vehicle of topical FMX-101, 4% administered daily for 12 weeks
- To evaluate the long-term safety of topical FMX-101, 4% administered daily for up to an additional 40 weeks

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The one-year study will have 2 parts. The first 12 weeks will be double-blind treatment with FMX-101, 4% or vehicle foam. The remaining 40 weeks will involve open-label treatment with FMX-101, 4% by any subjects who complete the first part of the study.

4.1.1. Part 1 – Double-blind

This is a randomized, multicenter, double-blind, vehicle-controlled, 2-arm study to evaluate the safety and efficacy over 12 weeks of FMX-101 minocycline foam, 4%, compared to vehicle, in the treatment of subjects with moderate to severe facial acne vulgaris.

Qualified subjects will be randomized to receive 1 of the following 2 treatments:

- FMX-101, 4% minocycline foam
- Vehicle foam

Subjects with qualifying lesion counts (Section 8.1.2) and Investigator's Global Assessments (IGA, Section 8.1.1) of acne severity scores and will be assigned to 1 of 2 treatments according to the randomization schedule. Subjects will apply the assigned study drug topically once daily for 12 weeks as directed. Subjects will be advised to apply the study drug at approximately the same time each day, preferably in the evening before bedtime. Both the Investigator and subject will be blinded to the study drug identity.

Subjects will return for visits at Weeks 1, 3, 6, 9, and 12. Efficacy evaluations (acne lesion counts and IGAs will be performed at Weeks 3, 6, 9, and 12 during the study. Other assessments will be performed as described in Sections 8.2 and 9.

4.1.2. Part 2 – Open-label

At the Week 12 Visit, subjects whose IGA score has not worsened may be invited to continue into the open-label part of this study for an additional 9 months of treatment. Subjects will be enrolled in this phase of the study until a total of approximately 400 subjects from Studies FX2014-04 and FX2014-05 have elected to continue in the open-label portion of their respective study. Subjects who elect to continue into the open-label part of this study will receive supplies of active FMX-101, 4% minocycline foam.

Treatment during this part of the study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment of some or all areas if there is clinical improvement or resolution of the acne in those areas. Even if the treatment is partially or completely temporarily suspended, the subject will continue in the study and make all scheduled clinic visits. If at any time the acne recurs or worsens, treatment of the affected areas may be resumed.

Subjects may be discontinued from the study after 12 weeks if their disease becomes refractory or they become intolerant of the product.

4.2. Rationale for Study Design and Dose Selection

A randomized, multicenter, double-blind, vehicle-controlled study design has been selected in order to assess the efficacy of the study drug in accordance with the FDA Guidance.[2] The subjects will be selected according to predefined entry criteria. The study will have a 12-week treatment duration.

FMX-101 foam, 4% is a novel minocycline formulation that has been shown to have efficacy in once daily use in a Phase 2 study. The once daily dosing regimen is appropriate given the pharmacokinetic characteristics of FMX-101, 4%.

Because of the mode of action of tetracycline drugs, the primary efficacy endpoints will be the effect on inflammatory lesion count and IGA (Section 8.1.1). The effect on noninflammatory lesions will be the most important secondary endpoint.

The extension of the study for an additional 40 weeks is necessary to obtain safety information about the long-term use of FMX-101, 4% to treat acne, which is a chronic condition. The design of the study is expected to provide sufficient safety information to fulfill the ICH E1 guideline.

5. STUDY POPULATION

The planned enrollment is 450 subjects. Subjects will be randomized to active or vehicle in a 2:1 ratio. Approximately 300 and 150 subjects will be assigned to the FMX-101, 4% or vehicle treatment groups, respectively.

5.1. Inclusion Criteria

A male or female subject will be considered eligible for participation in the study if all of the following inclusion criteria are satisfied prior to randomization:

1. Has completed and signed an appropriately administered Informed Consent Form (ICF) prior to any study-related procedures. Subjects less than 18 years of age (or as required by state law) must sign an Assent Form for the study and a parent or legal guardian must sign the ICF.
2. Is 9 years of age or greater,
3. Has facial acne vulgaris with:
   - 20 to 50 inflammatory lesions (papules, pustules, and nodules)
   - 25 to 100 noninflammatory lesions (open and closed comedones)
   - No more than 2 nodules on the face
   - IGA score of moderate (3) to severe (4)
4. If women of child-bearing potential, have a negative urine pregnancy test
5. For women of child-bearing potential at risk of becoming pregnant, agree to an effective method of contraception (Sections 7.7 and 7.8)
6. Willing to use only the supplied non-medicated cleanser CCI and to refrain from use of any other acne medication, medicated cleanser, excessive sun exposure, and tanning booths for the duration of the study

5.2. Exclusion Criteria

Subjects who have any of the following will be excluded from the study:

1. Female who is pregnant or lactating, or is planning a pregnancy during the study
2. Acne conglobata, acne fulminans, secondary acne (chloracne, drug induced acne) or any dermatological condition of the face or facial hair (eg, beard, sideburns, mustache) that could interfere with the clinical evaluations

3. Sunburn on the face
4. Severe systemic disease, which might interfere with the conduct of the study or the interpretation of the results.
5. Abnormal baseline laboratory values that are considered clinically significant.
6. Currently participating, or has participated within 30 days prior to this study, in an investigational drug or device study
7. Inability to fully comply with the study requirements

Subjects who have a history of any of the following will be excluded:

8. Allergy to tetracycline-class antibiotics or to any ingredient in the study drug
9. Pseudomembranous colitis or antibiotic-associated colitis
10. Hepatitis or liver damage or renal impairment
11. Known or suspected premalignant or malignant disease (excluding successfully treated skin cancers)
12. Subjects who have used the following medications (topical refers only to the facial area) will not be eligible:

    Within 1 week prior to randomization:

    - Medicated facial cleansers
    - Topical acne treatments (other than those listed below)

    Within 4 weeks prior to randomization:

    - Topical retinoids
    - Topical anti-inflammatories and corticosteroids
    - Systemic antibiotics
    - Systemic acne treatments

    Within 12 weeks prior to randomization:

    - Systemic retinoids
    - Systemic corticosteroids
13. Drug addiction or alcohol abuse (within the last 2 years).
14. Current or significant past history of depression.

6. STUDY PROCEDURES

Potential subjects will be assessed for eligibility at Screening. During this visit, the purpose, timing, procedures, and risks of the study will be explained to the subject, including requirements for enrollment and participation in the study, medication restrictions during the study, and requirements for washout of certain medications that the subject may already be taking.

The eligible subject who is willing to participate in the study will then sign an appropriately administered Informed Consent Form (ICF) prior to any study-related procedures. Subjects less than 18 years of age (or per state law) must sign an Assent Form for the study and a parent or legal guardian must sign the ICF.

Procedures at the Screening Visit will include obtaining blood and urine samples for clinical laboratory tests. These results must be no more than 30 days old at the time of Baseline Visit randomization.

If a subject, who has agreed to participate in the study and signed the ICF or Assent Form, is currently undergoing acne therapy identified in Exclusion Criterion 12, they must first enter a washout period, before beginning the Screening procedures.

A summary of study assessments and the time point at which they will be performed during the study is presented in Table 1. If a subject prematurely withdraws from the study before the Week 12 Visit, the subject should return to the study site for a withdrawal visit, during which all evaluations described under Visit 6/Week 12 must be performed.

See

Table 2 and Section 6.2 for descriptions of the procedures required during the open-label part of the study.

Table 1: Schedule of Procedures - Study FX2014-05 – Part 1

Assessment	Screening [1]	Baseline [1]	Visits				"Final" Visit [2]
Visit		**1**	**2**	**3**	**4**	**5**	**6**
Week			**1**	**3**	**6**	**9**	**12**
Informed Consent/Assent	X						
Demographic Data	X						
Assign identification number	X						
Medical/Surgical/Medication (prior/concomitant) History	X						
Inclusion/Exclusion criteria	X	X					
Physical Exam, height, weight [3,4]		X					X
Blood Pressure/heart rate [5]		X	X	X	X	X	X
Blood and urine samples for clinical laboratory tests	X			X			X
Urine pregnancy test (females of childbearing potential only)[6]		X		X	X	X	X
Investigator's Global Assessment	X	X		X	X	X	X
Lesion Count	X	X		X	X	X	X
Photography		X			X		X
Subject Satisfaction Questionnaire							X
Randomization		X					
Concomitant Medication		X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Tolerability Assessments			X	X	X	X	X
Perform drug accountability			X	X	X	X	X
Collect empty canisters			X	X	X	X	X
Dispense Study Drug		X	X	X	X	X	X[7]
Schedule/Confirm Next Visit	X	X	X	X	X	X	X

[1] The duration of Screening is variable but if there are medications to be discontinued it can not be less than the time indicated in Exclusion Criterion 12. The procedures required at these visits can be combined. However, **drug should not be dispensed until all inclusion and exclusion criteria are met.**

[2] Subject may continue into open-label phase of study. If a subject is not continuing into open-label phase for any reason (see Section 4.1.2, all evaluations described under Visit 6/Week 12 must be performed.

[3] Height to be measured only at Baseline

[4] Including 12-lead EKG at Screening in subjects over 39 years of age

[5] Measure blood pressure and heart rate after the subject has been sitting for at least 5 minutes at rest

[6] Perform urine pregnancy test at indicated visits. Also dispense home urine pregnancy test at Week 12 if subject is continuing into open-label treatment

[7] If subject is continuing into open-label treatment phase, dispense appropriate Study Drug Kit

6.1. Part 1 – Double-Blind

6.1.1. Screening Visit

- Obtain a signed and dated, written Informed Consent Form (ICF) prior to any study-related procedures; subjects less than 18 years of age (or as required by state law) must sign an Assent Form for the study and a parent or legal guardian must sign the ICF. (Subjects must be at least 9 years of age at the time of assent/consent)
- Obtain demographic data
- Assign the subject a unique subject identification number
- Obtain medical history
- Obtain surgical history
- Obtain history of prior and concomitant medication usage (including previous use of acne medications); record start and stop dates of any medications used in the last 3 months
- Perform IGA (Section 8.1.1)
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions (Section 8.1.2)
- Record regions beyond face affected by acne
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 9.6)
- If subject wears make-up, remind the subject not to wear any make-up at future visits.
- Record AEs
- Schedule/confirm the next study visit and remind subject to avoid overexposure to natural or artificial sunlight

6.1.2. Baseline Visit, Visit 1

The procedures required at this visit can be combined with Screening. However, drug should not be dispensed until all inclusion and exclusion criteria are met.

- Confirm/reconfirm eligibility according to the inclusion/exclusion criteria and
  - Perform IGA
  - Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Perform photography (Section 8.2)
- Measure blood pressure and heart rate (Section 9.4)
- Perform physical examination including height and weight (Section 9.5)

- Perform 12-lead EKG if subject is over 39 years of age
- Perform urine pregnancy test in females of childbearing potential
- Randomize the subject using the IWRS system, when all criteria have been met
- Record concomitant medications
- Record AEs
- Dispense 1 kit (2 canisters) of study drug
- Dispense cleanser CCI [redacted]
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight

6.1.3. Visit 2, Week 1

- Measure blood pressure and heart rate
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use properly; confirm that only provided cleanser is being used.
- Collect previously dispensed study drug canister(s) if applicable
- Dispense 1 kit (2 canisters) of study drug
- Schedule/confirm the next study visit and remind subject to avoid overexposure to natural or artificial sunlight

6.1.4. Visit 3, Week 3

- Measure blood pressure and heart rate
- Perform urine pregnancy test in females of childbearing potential
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 9.6)
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use properly; confirm that only provided cleanser is being used.
- Collect previously dispensed study drug canister(s) if applicable
- Dispense 1 kit (2 canisters) of study drug

- Determine if additional drug or cleanser needs to be dispensed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to natural or artificial sunlight

6.1.5. Visit 4, Week 6

- Measure blood pressure and heart rate
- Perform urine pregnancy test in females of childbearing potential
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Perform photography
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use properly; confirm that only provided cleanser is being used.
- Collect previously dispensed study drug canister(s) if applicable
- Dispense 1 kit (2 canisters) of study drug
- Determine if additional drug or cleanser needs to be dispensed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to natural or artificial sunlight

6.1.6. Visit 5, Week 9

- Measure blood pressure and heart rate
- Perform urine pregnancy test in females of childbearing potential
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use properly; confirm that only provided cleanser is being used.
- Collect previously dispensed study drug canister(s) if applicable
- Dispense 1 kit (2 canisters) of study drug
- Determine if additional drug or cleanser needs to be dispensed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to natural or artificial sunlight

6.1.7. Visit 6, Week 12 End of Double-Blind or Continuation in Open Label / Early Termination

- Perform physical examination including weight
- Measure blood pressure and heart rate
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory
- Perform urine pregnancy test in females of childbearing potential
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Perform photography
- Administer Subject Satisfaction Questionnaire
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use properly; confirm that only provided cleanser is being used.
- Collect previously dispensed study drug canister(s)
- If subject is continuing into the open-label phase of the study (see Section 4.1.2), dispense 2 kit (4 canisters) of FMX-101, 4% minocycline foam
    - If subjects facial acne is “clear” or “almost clear,” consider withholding treatment with FMX-101, 4% at this time but continue subject in study and schedule next visit.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to natural or artificial sunlight

6.2. Part 2 – Open-label

A summary of study assessments and the time point at which they will be performed during the Part 2 of this study is presented in

Table 2. If a subject prematurely withdraws from the study, the subject should return to the study site at which time all evaluations described under Final Visit 13/Week 52 must be performed.

Table 2: Schedule of Procedures - Study FX2014-05 – Part 2

Assessment	Visits						Final Visit [1]
Visit	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Week	**16**	**22**	**28**	**34**	**40**	**46**	**52**
Physical Exam, weight							X
Blood Pressure/heart rate [2]	X	X	X	X	X	X	X
Blood and urine samples for clinical laboratory tests			X				X
Urine pregnancy test (females of childbearing potential only)[3]	X	X	X	X	X	X	X
Investigator's Global Assessment	X	X	X	X	X	X	X
Lesion Count	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Tolerability Assessment	X	X	X	X	X	X	X
Subject Satisfaction Questionnaire							X
Perform drug accountability	X	X	X	X	X	X	X
Collect empty canisters	X	X	X	X	X	X	X
Dispense Study Drug	X	X	X	X	X	X	
Schedule/Confirm Next Visit	X	X	X	X	X	X	

[1] If a subject prematurely withdraws from the study, all evaluations described under Final Visit 13/Week 52 must be performed.
[2] Measure blood pressure and heart rate after the subject has been sitting for at least 5 minutes at rest
[3] Home pregnancy tests will be dispensed at each visit to all female subjects of a childbearing potential and will be performed at least monthly and whenever there is a suspicion of pregnancy (e.g., a missed period). Perform urine pregnancy test at Final visit.

6.2.1. Visit 7 - Week 16

- Measure blood pressure and heart rate
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use study drug properly
- Collect empty study drug canister(s)
- Dispense 2 kits (4 canisters) of FMX-101, 4% minocycline foam if required
- Dispense Home pregnancy kit to all female subjects of childbearing potential
- Schedule/confirm the next study visit and remind subject to avoid overexposure to natural or artificial sunlight
    - If subjects facial acne is "clear" or "almost clear," consider withholding treatment with FMX-101, 4% at this time but continue subject in study and schedule next visit.
    - If treatment has been interrupted, consider restarting treatment if clinically indicated

6.2.2. Visits 8, 9, 10, 11 and 12 – Weeks 22, 28, 34, 40 and 46

- Measure blood pressure and heart rate
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Record concomitant medications
- Record AEs and Tolerability Assessment
- At **Visit 9 (Week 28) only** - Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 9.6)
- Assess product use to confirm that subject continues to use study drug properly
- Collect empty study drug canister(s)
- Dispense 2 kits (4 canisters) of FMX-101, 4% minocycline foam if required
- Dispense Home pregnancy kit to all female subjects of childbearing potential
- Schedule/confirm the next study visit and remind subject to avoid overexposure to natural or artificial sunlight

- If subjects facial acne is "clear" or "almost clear," consider withholding treatment with FMX-101, 4% at this time but continue subject in study and schedule next visit.
- If treatment has been interrupted, consider restarting treatment if clinically indicated

6.2.3. Visit 13, Final Visit – Week 52

- Measure blood pressure and heart rate
- Perform physical examination including weight
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory
- Perform urine pregnancy test in females of childbearing potential
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Administer Subject Satisfaction Questionnaire
- Collect previously dispensed study drug canister(s)

7. STUDY TREATMENTS

FMX-101, 4% and vehicle will be supplied as identical canisters. All study drug will be stored, inventoried, reconciled, and destroyed according to US regulations.

7.1. Treatments Administered

The description of study drug kits and treatments is shown below.

7.1.1. Part 1 (double-blind) – Weeks 1 to 12

Dosage form description	Active kit: FMX-101 minocycline foam, 4%; Vehicle kit: Matching vehicle foam
Package description	Active kit: 2 canisters of FMX-101, 4% dispensed as foam when actuator is depressed Vehicle kit: 2 canisters dispensing vehicle foam when actuator is depressed
Daily dose	Approximately 0.5 gm of FMX-101, 4% (containing 40 mg minocycline per gram of foam; 0 mg for vehicle subjects); applied to face topically each day. Additional drug product may be applied to other acne-affected areas
Cumulative maximal dose	Approximately 1,680 mg of minocycline (0 mg for vehicle subjects) assuming application of 0.5 gm of foam daily to the face for 84 days. Maximum total amount of drug dispensed contains 14 gm of minocycline.
Dispensing	1 Kit (2 canisters) dispensed at Baseline and Weeks 1, 3, 6, and 9. Total of 5 kits (10 canisters) dispensed to the subject for the study.

7.1.2. Part 2 (open-label) – Weeks 13 to 52

Dosage form description	FMX-101 minocycline foam, 4%;
Package description	Active kit: 2 canisters of FMX-101, 4% dispensed as foam when actuator is depressed
Daily dose	Approximately 0.5 gm of FMX-101, 4% (containing 40 mg minocycline per gram of foam) applied to face topically each day. Additional drug product may be applied to other acne-affected areas
Cumulative maximal dose	Up to approximately 5,600 mg of minocycline assuming application of 0.5 gm of FMX-101 foam daily to the face for 280 days. Maximum total amount of drug dispensed contains 39.2 gm of minocycline.
Dispensing	Up to 2 Kits (4 canisters) dispensed at Weeks 12, 16, 22, 28, 34, 40 and 46 depending on rate of usage. Up to a total of 14 kits (28 canisters) dispensed to the subject for the study.

7.1.3. Dosing Instructions

7.1.3.1. Part 1 – Double-blind

The dosing regimen will be the same for both treatment groups.

After shaking the canister well, a small amount of foam (about 1/2 gram or a cherry-sized amount) should be expressed from the canister onto the fingertips of the hand and then rubbed into acne-affected parts of the face. This should be repeated as needed until all acne-affected parts of the face are treated. If acne is present on other parts of the subject's body (neck, shoulders, arms, back or chest) additional amounts (up to a total of 4g) of foam should also be applied to these areas. The foam should be applied at approximately the same time each day preferably in the evening at bedtime. The subject should not bathe, shower or swim for at least 1 hour after application of the product.

Study kits of blinded drug supplies will be dispensed at Baseline and Weeks 1, 3, 6 and 9 to ensure continuous dosing in case the subject is late for subsequent visits.

Dose adjustments are not permitted in this part of the study. Subjects who require a dose adjustment or discontinuation of study drug must be withdrawn from the study (Section 11.4).

7.1.3.2. Part 2 – Open-label

At the Week 12 Visit, subjects who elect to continue into the open-label part of this study will receive supplies of active FMX-101, 4% minocycline foam.

Treatment during this part of the study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment of some or all areas if there is clinical improvement or resolution of the acne in those areas. Even if the treatment is partially or completely temporarily suspended, the subject will be continued in the study and make all scheduled clinic visits. If at any time the acne recurs or worsens, retreatment of the affected areas may be resumed. At each visit, the changes in treatment will be documented.

Sufficient product will be dispensed at each visit to allow continuation of treatment as required. Subjects may be discontinued from the study at any time if their disease becomes refractory or they become intolerant of the product.

7.1.4. Manufacturer

The manufacturer of the investigational product is CCI [redacted]

7.1.5. Labeling of Study Drug

The Sponsor, or designee will label study drug supplies according to the requirements of the Code of Federal Regulations (21CFR§ 210, Subpart G-Packaging & Labeling Control).

The labels of the investigational (test) product will contain appropriate information as required by regional regulatory authorities and include, as needed, the following information:

- Name and address of the Sponsor
- Protocol number
- Product name / dosage form / mode of administration
- Kit Number / Canister Number
- Site number / Subject number
- Name and address of manufacturer
- Date of manufacture
- Lot/batch number
- Canister contents
- Storage conditions
- Caution Statements:
    - "New Drug – Limited by Federal Law to Investigational Use"
    - "Flammable"
    - "Shake well before use"
    - "Keep out of the reach of children"

The composition, pharmaceutical quality, batch number, and expiration date of the investigational (test) product will be traceable via the kit number.

7.1.6. Storage of Study Drug

FMX-101, 4% and vehicle canisters must be stored at 2°C – 8°C until being dispensed to the subjects. Subsequently, they must be stored at 20°C – 25°C (refer to USP Controlled Room Temperature). The investigator will be responsible for the suitable storage of the investigational product in compliance with the storage instructions and must restrict access to the study personnel only.

7.2. Study Drug Accountability

The Investigator will have overall responsibility for the use of the study drug. The Investigator or designee will verify the contents of the drug shipment and confirm receipt of the study drug in the Interactive Web Response System (IWRS) system. In addition, an accurate study drug dispensing record that specifies the date and amount dispensed to each subject must be kept. This inventory record must be available for inspection by representatives of the Sponsor and is subject to regional regulatory authority inspection at any time. At the conclusion of the study, the Investigator must provide a copy of this record to the Sponsor. In addition, the weight of each canister will be determined prior to being dispensed to the subjects and each canister that has been retrieved from the subject will be returned to the vendor to be weighed.

Under no circumstances will the Investigator allow the investigational drugs to be used other than as directed by this protocol. Qualified study personnel must use the IWRS to assign and dispense kits to the subjects. Reasons for digression from the expected dispensing regimen must also be recorded.

7.3. Handling and Disposal of Study Drug

The study drug must be protected from unauthorized access (eg, in a locked storage facility).

Any unused, partially used, or empty bottles of study drug will be returned to the Sponsor or designee by the time of the site's close-out visit. Receipt, distribution, and return of the study drug must be properly documented on forms provided by the Sponsor or designee.

7.4. Method of Assignment of Study Drug

7.4.1. Part 1 – Double- blind

After pretreatment clinical evaluations and all other screening procedures have been completed, authorized site personnel will acknowledge that the applicable subject met all the specified inclusion criteria and none of the exclusion criteria. Assignment to a treatment group will then follow a predetermined list of randomization numbers, with each successive number receiving 1 of the 2 treatments in random order. Authorized site personnel will use the IWRS system to assign a kit number that corresponds to the randomization schedule. The kit box with the assigned kit number will be dispensed to the subject.

The randomization code will be provided by TKL.

7.4.2. Part 2 – Open-label

All subjects who elect to continue into the second part of the study will receive FMX-101, 4% minocycline foam as described in Section 7.1.3.2.

7.5. Selection and Timing of Doses in the Study

The 4% minocycline concentration of FMX-101 was shown to be more effective than 1% in a Phase 2 study. The once-daily dosing regimen is appropriate given the pharmacokinetic characteristics of minocycline.

7.6. Blinding

The first part of this study is double-blind with limited access to the randomization code. The randomization code will be held in confidence until after the study database is locked and a memo documenting the database lock has been issued. Every effort will be made to retain the integrity of the blind. When issued to the sites, the study drug will be identical in appearance for all subjects, regardless of treatment assignment.

The treatment each subject receives will not be disclosed to the Investigator, study site personnel, subjects, monitors, or the Sponsor staff except as required for the purposes of conducting this study.

In the event that emergency identification of study drug is required (eg, if the Investigator believes that the information is necessary to properly treat a subject with an AE), the study drug identity can be obtained by the Investigator through the IRT system.

Before breaking the blind for a subject, the Investigator should determine that the information is necessary (ie, that it will alter the subject's immediate course of treatment and will contribute to the management of the AE). In many cases, particularly when the emergency is clearly not related to study drug, the problem may be effectively managed by assuming that the subject is receiving active study drug without the need for unblinding. Every effort should be made to alert the Medical Monitor before requesting that the blind be broken. If this is not possible, the Medical Monitor should be immediately notified of the breaking of the blind. The Investigator will record the unblinding procedures in the subject's source documents.

If unblinding is necessary, the subject will be withdrawn from the study and Week 12 Visit assessments will be completed.

7.7. Prior and Concomitant Therapy

Subjects should use the cleanser, CCI [redacted] (provided by the Sponsor). An alternative, non-medicated, cleanser may be used if agreed to by the Sponsor.

The use of or change in the dose of any and all concomitant medication, either prescription or over-the-counter, during the study will be recorded. The reason for use or change of dose of a concomitant therapy may need to be reported as an AE. Therapies (medication and non-medication therapies) not restricted by the protocol may be used. Non-prohibited chronic therapies being used at Baseline may be continued. If a subject is using an oral contraceptive product, she should have been on the same product for at least 3 months and she should continue using the same or equivalent product for the duration of the double-blind portion of the study.

If a subject is taking anticoagulant therapy, the subject should be advised that they may require a downward adjustment of their anticoagulant dosage.

All topical or systemic medications listed in the exclusion criteria are prohibited during the double-blind part of this study (through Week 12). Similarly, no other topical medications are permitted to be used on the face during this period. Subjects requiring systemic antibiotics not known to affect acne will be considered on a case-by-case basis.

During the open-label part of the study, concomitant acne medications are permitted; their use should be properly recorded. Benzoyl peroxide (e.g., Pro-Activ, Clearasil) can inactivate

minocycline and may thus decrease the effectiveness of FMX-101 if the two products are applied at the same time. Treated areas should be washed between applications of FMX-101 and products containing benzoyl peroxide. Preferably, the products should be applied no less than 8 hours apart.

See the Investigators' Brochure for information about tetracyclines and possible drug-drug interactions

7.8. Use of Contraception

Tetracycline-class antibiotics can cause fetal harm when administered to a pregnant woman. Tetracycline-class antibiotics used during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of teeth (yellow-gray-brown).

Prior to study enrollment, females of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. Females of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea > 12 consecutive months). Females of childbearing potential must have a negative urine pregnancy test and, if they are sexually active or become sexually active during the study, must use an effective method of birth control such as those listed below during the course of the study. The following is not an all-inclusive list; the subject must discuss with the Investigator the most appropriate form of birth control:

- Hormonal methods
    - Oral contraceptives – (Topical antibiotics may lessen the effectiveness of oral contraceptives. Therefore, a second form of birth control must be utilized in subjects using oral contraceptives)
    - Implant
    - Injection
    - Transdermal patch
    - Intravaginal Ring
- Intrauterine Device (hormonal or non-hormonal)
- Barrier methods
    - Condom (male or female) with spermicide
    - Diaphragm with spermicide
- Abstinence

7.9. Treatment Compliance

Each subject is to be instructed on the importance of following the dosing schedule and returning all kits (empty/used/unused) at the appropriate visits. The study personnel will question the

subject on the history of study drug use since the last visit. A subject who deviates significantly from the prescribed dosage will be counseled.

8. EFFICACY ASSESSMENTS

8.1. Primary Efficacy Assessments

The primary efficacy assessments will be the IGA and lesion counts.

8.1.1. Investigator Global Assessment Score (IGA)

Table 3 displays the IGA scale for acne vulgaris, which will be used by the investigators to assess the severity of a subject's acne vulgaris. The Case Report Forms (CRFs) will allow for Investigators to report lesions worsening beyond Grade 4 with treatment. The IGA must be performed prior to the lesion count.

The same evaluator should perform all evaluations for a subject; when this is not possible, another approved evaluator may perform the evaluations.

Table 3: IGA Scale for Acne Vulgaris

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions may be present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink- red)
2	Mild	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Many noninflammatory 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
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

8.1.2. Lesion Counts

Subjects are eligible for enrollment if they have:

- 20 to 50 inflammatory lesions (papules, pustules, and nodules)
- 25 to 100 noninflammatory lesions (open and closed comedones)
- No more than 2 nodules can be present on the face at Screening

Lesions will be characterized as inflammatory or non-inflammatory using the following criteria:

- **Inflammatory** lesions:

  Papule – a solid, elevated lesion less than 0.5 cm in diameter

  Pustule – an elevated lesion containing pus less than 0.5 cm in diameter

Nodule – palpable solid lesion greater than 0.5 cm in diameter; has depth, not necessarily elevated

- **Noninflammatory** lesions:

  Open comedones (blackhead) – non-infected plugged hair follicle with dilated/open orifice; black in color

  Closed comedones (whitehead) – non-infected plugged hair follicle: small (microscopic) opening at skin surface

Facial lesion counts will be made for the forehead, left and right cheeks, nose and chin at each visit. Total inflammatory lesions (pustules, papules, and nodular lesions) and noninflammatory lesions (open and closed comedones) will be counted and recorded separately. Lesion counts will be repeated at Weeks 3, 6, 9 and 12.

8.2. Photography

Photography of the face will be performed at Baseline and at Weeks 6 and 12 using recognized methods. The equipment and techniques for this photography and for archiving the images are described in the Study Manual. Photographs will be reviewed at the site and by the sponsor for quality. Photographs will not be used to assess the lesion counts or the Investigator's assessment of global severity but will be archived to be available for subsequent review, if required, by the sponsor, auditors or the FDA.

8.3. Subject Satisfaction Questionnaire

A satisfaction questionnaire will be administered at Visit 6, Week 12 and Visit 13, Week 52 (see Section 16.1, Appendix 1).

9. SAFETY ASSESSMENTS

The safety assessments in this study are standard safety measures in clinical studies, including physical examinations, the monitoring of vital signs, AEs (volunteered, observed, and elicited by general questioning in a non-suggestive manner), and clinical laboratory test results. In addition, skin assessments at the drug application site(s) will be performed.

9.1. Medical/Surgical History

A complete medical and surgical history will be obtained at Screening, which will include diseases of the head, ears, eyes, nose and throat; respiratory diseases; cardiovascular diseases; gastrointestinal diseases, hepatic diseases, genitourinary diseases, musculoskeletal diseases, endocrine diseases, neurological diseases, psychiatric diseases, skin diseases, allergies, hematological diseases, and other abnormalities.

9.2. Medication History

A history of medication usage (including previous use of acne medications and non-medication therapies) will be recorded at Screening. The start and stop dates of previous use of medications in the last 3 months will be recorded.

9.3. Concomitant Medications

All medication that the subject is currently taking or any change in medication or dosage since the last visit will be documented throughout the study.

9.4. Vital Signs

Heart rate and blood pressure will be measured at all post-Baseline visits. All blood pressure measurements will be made using a sphygmomanometer with an appropriate cuff size for the individual subject. Measurements will be administered while the subject is seated after at least 5 minutes at rest.

9.5. Physical Examination

A complete physical examination will include an evaluation of general appearance, skin, HEENT, neck, lymph nodes, lungs, heart, abdomen, musculoskeletal system, and neurologic system. A standard 12-lead EKG (after at least 5 minutes rest) will be performed at Baseline in subjects over 39 years of age.

Weight will be recorded at the Baseline Visit, Visit 6 (Week 12) and Final Visit (Week 52). Height will be measured at Baseline, only.

9.6. Clinical Laboratory Tests

Serum chemistry, hematology and urinalysis will be evaluated at Baseline, Week 12/ Final Visit of the double-blind phase of the Study, and at Week 28 and Week 52/Final Visit of the open-label phase of the Study. Serum chemistry, hematology, and urinalysis tests will be performed at a central laboratory.

Refer to the manual from the central laboratory for detailed instructions on collecting, processing, and shipping of samples.

Hematology	Urinalysis	Serum chemistry
Hematocrit Hemoglobin MCH MCHC MCV MPV Platelet count RBC RDW WBC Reticulocyte count WBC differential (% & absolute) : Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Glucose Ketones Leukocytes esterase pH Protein Specific gravity Urine pregnancy performed at the site	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartic acid transaminase (AST) Blood urea nitrogen (BUN) Calcium Chloride Cholesterol Creatinine Creatinine kinase Gamma glutamyl transferase (GGT) Globulin Glucose Phosphorus Potassium Sodium Total bilirubin (if elevated obtain direct bilirubin) Total protein Triglycerides Uric acid

9.6.1. Urine Pregnancy Test

A urine pregnancy test will be performed on all females of childbearing potential at Baseline, Week 3, Week 6, Week 9 and Week 12 of the double-blind phase of the Study and Final Visit or when a subject prematurely withdraws from the study.

Home pregnancy kits will be provided at each visit to all female subjects of childbearing potential in the open-label phase of the Study and are to be used at least monthly and if a pregnancy is suspected between visits (e.g., if a subject misses a period). A urine pregnancy test will be performed at Week 52/ Final Visit.

9.6.2. Sample Collection, Storage, and Shipping

Sample collection kits, requisition slips, and shipping boxes will be supplied by the central laboratory. Sample collection procedures and shipping instructions will be detailed in the laboratory manual. Study centers must be equipped to store the samples according to the laboratory manual procedures before shipping samples to the central laboratory.

9.7. Other Safety Measurements

9.7.1. Tolerability

Erythema, dryness, hyperpigmentation and skin peeling at the sites of study drug application will be assessed by the investigator at each study visit on a scale of 0 to 3 (0=none; 1=mild; 2=moderate; 3=severe). Itching will be assessed using the same scale based on the subjects' subjective assessment. The intensity and location of each finding will be recorded. These signs and symptoms should not be recorded as AEs unless they require concomitant treatment or lead to the subject's discontinuation from the study.

9.8. Adverse Events

9.8.1. Method of Determining Adverse Events

Safety assessments will include recording AEs reported spontaneously by the subject or observed by the Investigator. AEs will be recorded at each visit throughout the study on the appropriate CRF. Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

Subjects should be asked whether, since the time of the last observation or visit, they had any of the following:

- Experienced any changes in well-being
- Used any new medications
- Changed medication regimens (both prescription and over-the-counter)
- Were admitted to a hospital or had any accidents
- Developed unusual headaches or changes in vision

With the exception of the last item above, all questions should be of a general nature and should not suggest symptoms.

When an AE is suspected, all relevant evaluations will be carried out and appropriate treatment provided. Additional follow-up will be done as necessary (Section 9.8.4) and recorded in the subject's source documents, and the results will be provided to the Sponsor.

For AE definitions and reporting requirements, refer to Section 9.8.2 and Section 9.8.3, respectively.

9.8.2. Adverse Event Definitions

9.8.2.1. Adverse Events

An adverse event (AE) is any unfavorable or unintended sign, symptom, or disease that appears or worsens in a subject after the subject signs the ICF (and/or Assent Form) for a clinical study.

Examples of what may be considered an AE include any of the following:

- A new illness
- An exacerbation of a sign or symptom of an underlying condition or of a concomitant illness unrelated to participation in the clinical study or an effect of the study drug or comparator drug

No causal relationship with the study drug is implied by the use of the term "adverse event." An exacerbation of a pre-existing condition/illness is defined as a more frequent occurrence or as an increase in the severity of the pre-existing condition/illness during the study. Planned or elective surgical procedures for pre-existing conditions that have not worsened are not AEs. However,

any complication that occurs during a planned or elective surgery is an AE. (If the event meets the criteria for a serious adverse event [SAE], such as an extended hospitalization, it will be considered an SAE). Conditions leading to unplanned surgical procedures may also be AEs.

9.8.2.2. Serious Adverse Events

A "serious adverse event" (SAE) is any AE that:

- Results in death
- Is life-threatening
  (Note: The term "life-threatening" refers to any AE that, as it occurs, puts the subject at immediate risk of death. It does not refer to an AE that hypothetically might have caused death if it were more severe.)
- Results in hospitalization or prolongation of current hospitalization (not including hospitalization for a pre-existing condition that has not increased in severity or frequency from the subject's underlying medical condition prior to entry into the study)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of a subject
- Is another serious (important medical events) events

(Note: Important medical events may not be immediately life-threatening or result in death or hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed 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 development of drug dependency or drug abuse.)

SAEs will be reported by the Sponsor to the regulatory authorities as required.

9.8.2.3. Severity of Adverse Events

"Severity" of the AE refers to the extent to which an AE affects the subject's daily activities and differs from "Serious," which is a regulatory classification. Severity will be categorized according to the following criteria:

- **Mild**: The symptom has a negligible effect or no impairing effect on the subject's normal function.
- **Moderate**: The symptom impairs the subject's normal function to some extent.
- **Severe**: The symptom has an obvious, significantly impairing effect on the subject's normal function.

9.8.2.4. Relationship of Adverse Events to Study Treatments

"Causality" refers to the relationship of the AE to study drug and will be categorized according to the following criteria:

- **Unlikely**: There is no medical evidence to suggest that the AE may be related to study drug usage, or there is another more probable medical explanation.
- **Possible**: There is medical evidence to suggest that there is a reasonable possibility that the AE may be related to study drug usage. However, other medical explanations cannot be excluded as a possible cause.
- **Probable**: There is strong medical evidence to suggest that the AE is related to study drug usage.

9.8.2.5. Adverse Events Expectedness

Expected AEs are defined as those described in the Investigator's Brochure. If an event increases in intensity or severity from that described in the IB, it will be considered unexpected.

9.8.3. Reporting Adverse Events

AEs that occur from the time of informed consent/assent through completion of the last study visit should be reported. Any AE that the Investigator becomes aware of that occurs within 30 days of study completion or withdrawal should also be reported.

Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

Any serious AEs occurring in a subject receiving study drug must be reported to the Sponsor or designee within 24 hours of the site being informed of the event, even if the event does not appear to be drug-related. The report must be made by sending a completed Serious Adverse Event (SAE) Report form to the Sponsor or designee. Any pertinent follow-up information should be provided in a similar manner. Contact information is provided below:

TKL Clinical Pharmacovigilance
CCI [redacted]

9.8.4. Adverse Event Follow-up

Adverse events, and tolerability signs and symptoms greater than zero (0), that are ongoing when a subject withdraws from or completes the study will be followed until resolution or stabilization (in the opinion of the Investigator), or for 30 days, whichever is shorter. Investigators and the Sponsor will decide if longer follow-up is appropriate on a case-by-case basis. Subjects who experience any clinically significant AE will remain under medical supervision until the Investigator or the Sponsor's Medical Monitor deems the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up.

Laboratory values that are abnormal and not assessed as AEs may be followed at the discretion of the Investigator or the Sponsor's Medical Monitor until resolved or stabilized.

9.8.4.1. Pregnancy reporting

Prior to study enrollment, females of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The Informed Consent or Assent Form that the subject signs must document this discussion.

If a subject or Investigator suspects that the subject may be pregnant prior to study drug administration, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study drug and must not be enrolled in the study.

A urine pregnancy test will be performed on all females of childbearing potential at Baseline, Week 3, Week 6, Week 9 and Week 12 of the double-blind phase of the Study and Final Visit or when a subject prematurely withdraws from the study.

Home pregnancy kits will be provided at each visit to all female subjects of childbearing potential in the open-label phase of the Study and are to be used at least monthly and if a pregnancy is suspected between visits (e.g., if a subject misses a period). A urine pregnancy test will be performed at Week 52/Final Visit.

During the study, all females of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period). If a subject or Investigator suspects that the subject may be pregnant at any time before or during the study, the study drug must be withheld until the results of laboratory pregnancy testing are available. The Sponsor and Site Monitor must be notified and available information captured on a "Suspected Pregnancy" form. If pregnancy is confirmed, the subject must be withdrawn from the study and the Sponsor and Site Monitor notified. Additional relevant information about the confirmed pregnancy will be recorded on the appropriate form(s) but the pregnancy will not be captured as an AE.

The subject should be followed until the outcome of the pregnancy is known.

9.8.5. Clinically Significantly Abnormal Laboratory Results

All laboratory values that are outside of the normal range for that parameter will be so flagged when reported to the site. The Investigator will determine which out-of-range laboratory test results should be characterized as clinically significant and will so annotate the laboratory report. If a clinically significant laboratory abnormality requires treatment or is the reason for a subject being discontinued from the study, the abnormal result must also be classified as an AE.

9.9. Appropriateness of Safety Measurement

The safety assessments in this study are standard safety measures in clinical trials.

10. STATISTICAL DESIGN AND ANALYSIS

10.1. Statistical Analysis Plan

A detailed statistical analysis plan will be finalized prior to breaking of the study blind.

Descriptive statistics for qualitative variables (eg, race) will include the number and percentage of subjects with the qualitative response. Missing responses will be enumerated, but the calculation of percentages will exclude missing responses. For quantitative variables (eg, age), descriptive statistics will include the number of subjects with non-missing data, mean, standard deviation, median, minimum value and maximum value. All hypothesis testing will be conducted using two-sided tests with α=0.05 level of significance unless otherwise specified.

All study data will be presented in listings.

10.2. Determination of Sample Size

In a phase 2 study, the proportion of subjects with an IGA score of 0 or 1 after 12 weeks of treatment was CCI in the minocycline 4% foam group compared to 2% in the vehicle group. The following table provides a few alternate assumptions and corresponding sample sizes. Power was set to CCI and type-1 error to two-sided 0.05. Sample size was calculated based on Fisher's Exact test.

Vehicle IGA (0,1)	Minocycline 4% foam IGA (0,1)	Sample sizes (vehicle, active)
CCI	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI

Assuming 12% dropout rate, 300 subjects on active, and 150 subjects on vehicle will provide at least CCI power for a statistically significant difference on IGA 0 or 1. In the same phase 2 study, the change from baseline in inflammatory lesions was CCI in the minocycline 4% foam versus CCI in the vehicle group. The standard deviation in change from baseline was approximately CCI The following table shows alternate assumptions and corresponding sample sizes, for 90% power and a two-sided type 1 error of 0.05. The sample sizes were calculated using a t-test.

Vehicle mean inflammatory lesion reduction	Minocycline 4% foam mean inflammatory lesion reduction	Sample sizes (vehicle, active)
CCI	CCI	CCI
CCI	CCI	CCI
C	CCI	CCI

To summarize, using some conservative estimates of the effect on minocycline 4% foam versus the vehicle for both IGA and change in inflammatory lesions at week CCI subjects on active, and 150 on vehicle will provide > 90% power for s statistically significant difference.

Another consideration for the sample size must be given to the secondary endpoint of noninflammatory lesions which will be compared to the vehicle for non-inferiority. The margin for non-inferiority will be CCI f the change from baseline to week 12. In a phase 2 study, change from baseline in noninflammatory lesions at week 9 was CCI for the vehicle group with a standard deviation of 18. Assuming approximately the same reduction at week 12, a CCI non-inferiority margin is about CC lesions. The following table provides approximate sample sizes for alternate assumptions for 90% power to show non-inferiority.

Vehicle mean noninflammatory lesion reduction	Minocycline 4% foam mean noninflammatory lesion reduction	Sample sizes (vehicle, active)
CCI	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI

If Minocycline 4% foam has the same effect on noninflammatory lesions as vehicle, CCI subjects on vehicle and CCI on 4% foam will be needed for 90% power to show non-inferiority. If Minocycline 4% foam has a slightly less effect on noninflammatory lesions (CCI lesion reduction versus CCI in vehicle), there will be about 90% power to show non-inferiority.

10.3. Analysis Populations

The Intent-to-Treat (ITT) population will include all randomized subjects. The ITT population will be the primary population for all efficacy analyses.

The Safety population will include all randomized subjects who took at least one dose of study drug. Subjects who have no post-Baseline assessments will be included in the Safety population unless all dispensed study drug is returned unused.

The Per Protocol (PP) population is defined as the subset of the ITT population without any protocol deviations that may have an impact on the efficacy assessments. The subjects to be

included in the PP population will be determined by the Sponsor/CRO prior to the unblinding of the study. The PP population will be secondary for the co-primary endpoints only.

Subjects may be excluded from the PP population if any of the following are met:

- Did not meet inclusion/exclusion criteria
- Have administered any interfering concomitant medications
- Have not, in the opinion of the investigator, been compliant with the treatment regimen (e.g. reported frequent missed doses)

Prior to breaking the blind, additional criteria for exclusion from the PP population may be included to accommodate for unforeseen events that occurred during the conduct of the study.

10.4. Efficacy Endpoints

The primary population for all efficacy analyses will be the ITT population. Subjects will be analyzed according to their randomized treatment. The primary method of handling missing data will be the last observation carried forward (LOCF) approach. Sensitivity analyses using multiple imputations and baseline observation carried forward (BOCF) will be performed on the co-primary endpoints only.

Supportive efficacy analyses will also be performed on the PP population. All analyses using the PP population will use the Observed-Cases (OC) approach. i.e., there will be no imputation for missing data at any time point.

Changes from Baseline lesion count will be calculated as the Baseline value minus the post-Baseline value. Thus, a positive change will reflect a reduction in lesion count. The percent change from Baseline lesion count will be calculated as the Baseline value minus the post-Baseline value divided by the Baseline value, expressed as a percentage. Thus, a positive percent change will reflect a reduction in lesion count.

10.4.1. Primary Efficacy Endpoints

The co-primary efficacy endpoints are:

- The absolute change from Baseline in the inflammatory lesion count at Week 12
- Treatment Success (dichotomized as Yes/No) at Week 12, where success is defined as an IGA score of 0 or 1, and at least a 2-grade improvement (decrease) from Baseline

The null hypotheses of the equality of the FMX-101 4% and vehicle means for absolute change from Baseline to Week 12 in the inflammatory lesion count and the equality of IGA success rates at Week 12 will each be tested at a two-sided 0.05 level of significance. Change from baseline in inflammatory lesion count will be analyzed using an Analysis of Covariance (ANCOVA), with Treatment as a main effect, baseline inflammatory lesion count as a covariate, and investigational site a blocking factor. Investigational site by Treatment interaction will be tested at 0.1 level, and if significant, it will further be explored. The dichotomized IGA will be analyzed using a Cochran-Mantel-Haenszel (CMH) test, stratified by investigational site.

10.4.2. Secondary Efficacy Endpoints

- The absolute change from Baseline in the noninflammatory lesion count at Week 12
- The absolute change from Baseline in the inflammatory lesion count and IGA Treatment Success at the interim visit at Week 9
- The absolute change from Baseline in the inflammatory lesion count and IGA Treatment Success at the interim visit at Week 6

10.4.3. Tertiary efficacy endpoints

- The percent change from Baseline in the inflammatory lesion count at Weeks 3, 6, 9 and 12
- The absolute change from Baseline in the inflammatory and noninflammatory lesions, and the IGA Treatment Success at Week 3
- The absolute change from Baseline in the noninflammatory lesion count at Weeks 3, 6, 9 and 12
- The percent change from Baseline in the noninflammatory lesion count at Weeks 3, 6, 9 and 12

Secondary efficacy endpoint will be tested sequentially in the order listed above, at 0.05 level of significance, only if the co-primary efficacy endpoints are significant.

10.5. Safety endpoints

Treatment-emergent adverse events (TEAEs), vital signs, physical examinations, and clinical laboratory measurements will be reported on the Safety population. Subjects will be reported according to the treatment they actually received. No statistical tests will be performed for any of the safety assessments.

Baseline for vital signs, physical examinations, and clinical laboratory measurements is defined as the last non-missing value prior to the first dose of study drug.

10.5.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) terminology will be used to classify all AEs with respect to system organ class (SOC) and preferred term.

TEAEs will be defined as events that emerge during treatment having been absent pre-treatment, or worsen relative to the pre-treatment state. Summaries of AEs will be limited to TEAEs. The number and percentage of subjects reporting each SOC and preferred term will be summarized for each treatment group and by the Study Period. At each level of summarization, a subject will be counted once if he/she reported one or more events. The severity of TEAEs and relationship to study drug will be summarized in a similar manner. For summaries of relationship to study drug, a subject will be classified according to the closest relationship. For summaries of TEAE severity, a subject will be classified according to the highest severity.

Summaries of SAEs and subjects who prematurely withdraw from the study due to AEs will be presented.

10.5.2. Vital Signs

Vital sign parameters will be summarized using descriptive statistics at Baseline and at each post-baseline time point. Changes from Baseline will also be summarized. Baseline is defined as the last non-missing value prior to the first dose of study drug.

10.5.3. Physical Examinations

Physical examinations will be summarized using descriptive statistics at Baseline and at each post-baseline time point. Shifts from Baseline will also be summarized. Baseline is defined as the last non-missing value prior to the first dose of study drug.

10.5.4. Clinical Laboratory Results

Baseline is defined as the last non-missing value prior to the first dose of study drug.

Shift tables for each clinical laboratory test will cross-tabulate the number of subjects with values below the laboratory reference range (low), values within the laboratory reference range (normal) or above the laboratory range (high) at baseline with the number of subjects with low, normal or high values at each post-baseline time point.

A listing of subjects with pre-treatment and treatment-emergent clinically significant abnormal laboratory values will be presented for each treatment group. Clinical significance is based on the Investigator's judgment.

10.6. Statistical Analysis

10.6.1. Interim Analysis

No interim analysis is planned.

10.6.2. Subject Accounting, Demographic, and Baseline Characteristics

Demographic, baseline characteristics, and prior and concomitant medications will be summarized by treatment. Study completion status and reasons for discontinuation will also be displayed by treatment.

Medical and surgical history will only be presented in the listings.

10.6.3. Efficacy Analysis

The co-primary endpoint of absolute change from Baseline in inflammatory lesions at Week 12 will be analyzed using an Analysis of Covariance (ANCOVA) model with main effect treatment and investigational site as a covariate. The treatment by investigational site interaction will be tested separately at 0.1 level of significance, and if significant, will be further be explored. A 95% confidence interval will be calculated on the difference in mean changes from baseline between FMX-101 4% and vehicle.

The co-primary endpoint of IGA Treatment Success rate at Week 12 will be analyzed using a Cochran–Mantel–Haenszel (CMH) test with investigational site as the stratification factor. If the overall IGA Treatment Success rate is less than 10%, a Fisher's Exact test will be used to

corroborate the CMH test. A 95% confidence interval will be constructed on the difference in IGA Treatment Success rates between FMX-101 4% and vehicle.

If FMX-101, 4% is found superior to vehicle (one-sided p<=0.025) for both co-primary endpoints, the secondary endpoints will be tested sequentially. The first secondary endpoint of noninflammatory lesions at Week 12 will be tested initially as a non-inferiority comparison of FMX-101, 4% to vehicle. Non-inferiority margin is defined as 30% of the noninflammatory lesion reduction in the vehicle group at Week 12. A lower 97.5% confidence limit will be calculated for μ_a-0.6×$\mu_{v,}$ where μ_a and μ_v are the mean reduction of noninflamatory lesions of FMX-101, 4% and vehicle respectively. If the confidence limit is above 0, non-inferiority will be concluded. If non-inferiority is concluded, the superiority of FMX-101, 4% to vehicle for noninflammatory lesions at Week 12 will be tested. The sequential testing will proceed according to the order in Section 10.4.2.1. Testing of secondary efficacy endpoints at an earlier timepoint for each type of lesion and IGA Treatment Success will be performed only if superiority (one-sided p<=0.025) is seen at the later timepoint.

Secondary efficacy parameters will be analyzed similar to the appropriate co-primary efficacy parameter.

Absolute change from baseline in inflammatory lesion count and the IGA assessments in the open-label phase of the study will be summarized. No statistical testing will be performed for the open label efficacy data.

10.6.4. Safety Analysis

The Medical Dictionary for Regulatory Activities (MedDRA) terminology will be used to classify all AEs with respect to system organ class (SOC) and preferred term.

TEAEs will be defined as events that emerge during treatment having been absent pre-treatment, or worsen relative to the pre-treatment state. Summaries of AEs will be limited to TEAEs. The number and percentage of subjects reporting each SOC and preferred term will be summarized for each treatment group. At each level of summarization, a subject will be counted once if he/she reported one or more events. The severity of TEAEs and relationship to study drug will be summarized in a similar manner. For summaries of relationship to study drug, a subject will be classified according to the closest relationship. For summaries of TEAE severity, a subject will be classified according to the highest severity.

Summaries of SAEs and subjects who prematurely withdraw from the study due to AEs will be presented.

Vital sign parameters will be summarized using descriptive statistics at Baseline and at each post-baseline time point. Changes from Baseline will also be summarized.

Physical examinations will be summarized using descriptive statistics at Baseline and for the final visit. Shifts from Baseline will also be summarized.

Shift tables for each clinical laboratory test will cross-tabulate the number of subjects with values below the laboratory reference range (low), values within the laboratory reference range (normal) or above the laboratory range (high) at baseline with the number of subjects with low, normal or high values at the Final Visit.

A listing of subjects with pre-treatment and treatment-emergent clinically significant abnormal laboratory values will be presented for each treatment group. Clinical significance is based on the Investigator's judgment.

11. STUDY MANAGEMENT

11.1. Monitoring

The Investigator will be responsible for preparing and maintaining adequate and accurate source documents (medical records, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject treated with the study drug. The Investigator will allow representatives of the Sponsor, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study. The Investigator is to immediately notify the Sponsor or the Sponsor's representative of any regulatory authority inspections. The Investigator will be informed about the outcome of any Sponsor audit.

This study will be monitored regularly, by or under supervision of a monitor from the Sponsor. The frequency of monitoring visits will be agreed upon by the Sponsor's representative and the study site.

Monitoring visits will take place on a regular basis according to the enrollment rate and number of subjects enrolled at each investigational site. During these visits, the monitor will check the completion of the CRF entries, compliance with the study protocol and with GCP-ICH, and the agreement of key entries with the source data. The monitor will also verify the correct use of the study drug. At the Final Visit or at an agreed to time prior to the Final Visit, the monitor will check all remaining material including the remaining quantities of the study drug and will organize their return to the Sponsor or designee. At each visit, the Investigator and staff will be expected to cooperate with the Sponsor's representative(s) for the purposes of review and verification of protocol compliance, AE reporting, CRFs, source documents, clinical supplies and inventory records, and any additional records as may have been previously arranged between the Investigator and the Sponsor's representative(s).

The Investigator and/or other designated study personnel are expected to contact the Sponsor's or the Sponsor's representative's clinical research associate, as needed, regarding study concerns and/or questions. Contact information is provided in the Study Binder for the site.

11.2. Protocol Amendments

The Sponsor may propose to amend this protocol at any time.

No change to the protocol will be implemented until the Sponsor and the IRB have reviewed and approved the amendment.

In the event of an emergency, the Investigator shall implement any medical procedures deemed appropriate for subject safety. All such procedures must have written documentation and be promptly reported to the Sponsor.

Amendments to the protocol, if any, are included in Section 16.2, page 53. This protocol version includes Amendment 1, effective February 26, 2016 and Amendment 2, effective April 6, 2016.

11.3. Protocol Deviations

A protocol deviation is any change, divergence or departure from the IRB-approved protocol by the study staff (intentional or unintentional). All deviations are to be documented at the site and reported to the IRB according to the IRB's guidelines.

In the event of an emergency, the Investigator shall implement any medical procedures deemed appropriate for subject safety. All such procedures must have written documentation and be promptly reported to the Sponsor.

11.4. Withdrawal of Subjects

Withdrawn subjects are those who do not complete all evaluations and procedures outlined in the protocol. Subjects who discontinue taking study drug for any reason must also be withdrawn from the study. Subjects may be withdrawn from the study because of one of the following:

- **Adverse Event:** An AE that, in the opinion of the Investigator or Sponsor, suggests that continued participation in the study is not in the subject's best interest for safety reasons. All AEs that are present when the subject withdraws from the study will be followed as described in Section 9.8.4.
- **Abnormal Laboratory Result:** Any clinically significant laboratory abnormality that requires withdrawal of the subject from the study should be considered an AE leading to withdrawal. If possible, laboratory tests will be repeated for any results that were clinically significantly abnormal until the abnormality is resolved or stabilized to the satisfaction of the Investigator in consultation with the Medical Monitor.
- **Lost to Follow-up:** Confirmed at minimum by 2 phone calls and a traceable letter without response.
- **Subject Request:** Subject requests, for any reason (eg, AE), to be withdrawn or withdraws his/her consent.
- **Poor protocol adherence:** A subject may be withdrawn from the study at the discretion of the Investigator or Sponsor due to poor compliance with protocol requirements that may compromise the study results or subject safety.
- **Other:** Other reasons include but are not limited to: Investigator decision that it is in the subject's best interest to be withdrawn, administrative reasons, relocation of subject, etc. If a subject becomes pregnant during the study, the subject will be withdrawn from the study and followed through conclusion of the pregnancy.

If a subject is withdrawn from the study following the start of study drug during Period 1 of the study, all Week 12 assessments should be completed. If a subject is withdrawn from the study following the start of study drug during Period 2 of the study, all Final Visit assessments should be completed. Subjects withdrawn from the study will not be replaced.

11.5. Termination of the Study

The study may be terminated at any time at the request of the Sponsor or a regulatory authority, with proper and timely notification of all parties concerned. The IRB will be informed promptly and the Sponsor or the Investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements. Otherwise, the study is considered terminated upon completion of all subject treatments and evaluations.

11.6. Publication Policy

The data obtained in this study are the property of the Sponsor, which will make reasonable efforts to assure that the results are published in a peer-reviewed journal. As some of the information concerning the investigational product and development activities at the Sponsor may be of strictly confidential nature, any manuscript or other presentation of data must first be reviewed by the Sponsor before its submission.

12. ETHICS

12.1. Conduct of the Study

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP, 1997; the US Title 21 CFR parts 50, 56, and 312; and the ethical principles that have their origin in the Declaration of Helsinki. The study will not begin until all of the requirements of the appropriate regulatory authorities have been fulfilled.

12.2. Institutional Review Boards (IRB)

This protocol (and any changes), all consent/assent forms, and subject consent procedures must be reviewed and approved by a properly constituted IRB. The information presented to the IRB at the time initial approval is sought must include any plans for subject recruitment that involve advertising or other direct contact with potential subjects outside of the doctor-subject relationship. A letter of approval issued by the IRB must be sent to the Sponsor prior to initiation of the study. Any changes made to the protocol must be approved by the IRB prior to implementation, except where needed to eliminate a potential imminent safety hazard to the subjects. In this case, immediate implementation may apply place followed by IRB approval. Review and approval by the IRB for continuation of the study must apply place at least once a year.

12.3. Written Informed Consent

The Investigator or designee will explain the nature of the study, its purpose and associated procedures, the expected duration and the potential benefits and risks of participation to each subject prior to his/her entry into the study (ie, before examinations and procedures associated with selection for the study are initiated). Each subject will have ample opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Following this informative discussion, the subject will be asked if he/she is willing to sign a statement of informed consent. Only subjects who voluntarily sign the Informed Consent Forms (ICF) may enter the study. Subjects less than 18 years of age (or as required by state law) must sign an Assent Form for the study and a parent or legal guardian must sign the ICF.

The ICF and Assent Form must be reviewed and approved by the Sponsor and the IRB prior to their use.

The original signed ICF and Assent Form will remain in the Investigator's files. The Investigator or designee will indicate in each subject's source documents that he / she has informed the subject about the study and its procedures, the subject has signed and dated the ICF/Assent Form, and the subject has been given a copy of the documents. The Investigator or designee will inform subjects of any new information that may be relevant to the subjects' willingness to continue in the study.

12.4. Subject Confidentiality

The Sponsor ensures that the following have permission to review all study-related documents: monitor, auditor, IRB and regulatory authorities. The subject's identity and study-related records will remain confidential throughout the duration of the study data collection and reporting process.

A unique subject identification code is assigned to each potential study subject. The identification code protects the subject's identity and is used in lieu of the subject's name when reporting subject data. The data will always maintain the confidentiality of the subject.

The investigator or designee will review the subject data, which will be referenced using the subject identifier. At the conclusion of the study, the data obtained may be presented to regional regulatory authorities but the subject's identity will not be revealed. In addition, if any clinical data obtained from the study is published in scientific journals or presented at scientific meetings the subject's identity will not be revealed.

12.5. Records Retention

The Investigator must maintain essential study documents (protocol and amendments, source documentation corresponding to all information contained in the CRFs, signed informed consent and assent forms, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same time period. Custody of the records may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notice of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

12.6. Financing

Funding for this study will be agreed between the Investigator and the Sponsor and will be confirmed in writing before the study starts.

Completion of Financial Disclosure Forms will be required before the study starts. Any additions to the primary site personnel will necessitate the completion of new Financial Disclosure Forms. This information will also be collected at site closure and one year after the completion of the study.

Disclosure Forms. Investigators will be informed that they must report any new information to the sponsor or designate at site closure and one year after the completion of the study.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and Investigator will apply all steps possible to ensure the accuracy, consistency, completeness, and reliability of the data, including participating in an Investigator meeting and/or site initiation visit, routine site monitoring, review of CRFs against source documents, and quality control checks.

In addition, a representative from the Sponsor's Clinical Quality Assurance (CQA) Department or designee may conduct periodic audits of the study processes, including, but not limited to, auditing the clinical site, laboratories, vendors and CROs, the clinical database, and the final study report.

14. DATA HANDLING AND RECORD KEEPING

This study will use web-based, electronic case report forms (eCRFs) developed through a validated, Electronic Records / Electronic Signatures-compliant platform (US Title 21 CFR Part 11). Foamix Clinical Data Management department or designee will create the electronic CRFs and corresponding clinical database based on the final protocol.

All site personnel who will be using this system will receive formal training on the system, after which each person will be issued a unique user name and password. Only the person who owns the user name and password will enter the system using that user name and password. For data security reasons and to be in compliance with regulatory guidelines, usernames and passwords are not transferable.

The Investigator is responsible for all data entered via the eCRFs and must confirm the accuracy of the data by electronically approving (signing) the eCRFs. This responsibility includes the timely completion and accuracy of the data entered into the eCRFs by their site personnel as well as the review of some data entered directly into the database (eg, clinical laboratory results) by an external vendor. The Sponsor will review the database to identify data errors or inconsistencies, which will be posted in the RDC system as queries for resolution. In addition, the Sponsor may make obvious corrections to the data in the database (eg, obvious errors in dates) and so inform the Investigator without issuing a query to the site.

15. REFERENCE LIST

1. Brown SK, Shalita A R; Acne Vulgaris, Follicutitis, and Acne Rosacea. Lancet 351:1871-76, 1998
2. Guidance for Industry: “Acne Vulgaris: developing Drugs for Treatment ” September 2005 FDA Draft Guidance

16. APPENDICES

16.1. Appendix 1 – Subjects Satisfaction Questionnaire

The following 8 questions will be asked of the subject at Visit 6, Week12 and Visit 13, Week 52:

1. How satisfied are you with this product in treating your acne?
2. How satisfied are you with how easy this product is to use?
3. How satisfied are you with this product compared to other products you have previously used for acne, such as gels and creams?
4. How satisfied are you with how this product feels on your skin after treatment?
5. How satisfied are you with the odor of this product after treatment?
6. How satisfied are you with the color of this product after treatment?
7. Overall, how satisfied are you with this product?
8. Overall, how likely are you to recommend this product to a friend?

Answers to Questions 1-7 will be selected from the following:

1=Very Satisfied

2=Satisfied

3=Somewhat Satisfied

4=Dissatisfied

5=Very Dissatisfied

Answer to Question 8 will be selected from the following:

1=Very Likely

2=Likely

3=Somewhat Likely

4=Unlikely

5=Very Unlikely

16.2. Appendix 2 – Protocol Amendments

This appendix describes the amendment(s) that have been made to the protocol for Study FX2014-0.

Section 16.2.1 describes the changes made to Protocol FX2014-05 Version 1 issued January 19, 2016, via Amendment 1 effective February 26, 2016.

Section 16.2.2 describes the changes made to Protocol FX2014-05 Version 2 issued February 26, 2016, via Amendment 2 effective April 6, 2016.

Section 16.2.3 describes the changes made to Protocol FX2014-05 Version 3 issued April 6, 2016 via Amendment 3 effective October 14, 2016.

16.2.1. Amendment 1, effective February 26, 2016

The following is the summary of the changes that were made to Protocol FX2014-05 Version 1 issued 19-JAN-2016.

Administrative changes:

Section	Revision
Title Page	Added: PPD
Signature Page	Added
Study Administrative Structure	Added: PPD
SAE Reporting Information	Added: TKL Clinical Pharmacovigilance CCI

Content changes:

New or changed test is **bolded.**

Section	Revision		Rationale
	Old Text	New Text	
1.10.1. Efficacy	. . Weeks **1,** 3, 6, 9 and 12	. Weeks 3, 6, 9 and 12.	Correction
1.11 Statistical Methods	IGA **score at** Week 12 (where success is defined as **at least a 2-grade decrease from Baseline)**.	IGA **Treatment Success (dichotomized as Yes/No) at** Week 12, where success is defined as **an IGA score of 0 or 1, and at least a 2-grade decrease from Baseline.**	Modified as per FDA suggestion
	At least a 2-grade improvement (decrease) from Baseline in the IGA score will be analyzed using . . .	**The IGA Treatment Success rates will be compared between the treatment groups using . . .**	

Section	Revision		Rationale
	Old Text	**New Text**	
6. Study Procedures	Inserted	**Procedures at the Screening Visit will include obtaining blood and urine samples for clinical laboratory tests. These results must be no more than 30 days old at the time of Baseline Visit randomization.**	Clarification of timing of laboratory tests during Screening
6. Study Procedures – Table 1	Inserted	"**X**" for Tolerability Assessment at all post-Baseline visits	Added at request of FDA
	"**X**" for Blood and urine samples at Baseline	"**X**" for Blood and urine samples at Screening	Sampling moved to earlier timepoint
	Inserted	"**X**" for Blood and urine samples at Week 3	Added at request of FDA
	Inserted	"**X**" for Dispense study drug at Week 1	Correction
	Inserted	"**X**" to Confirm next visit	Correction
	Footnote inserted	Footnote 6 - **Home pregnancy tests will be dispensed to all female subjects at risk of becoming pregnant and will be performed whenever there is a suspicion of pregnancy (e.g., a missed period)**	Added at request of FDA
6. Study Procedures – Table 1 Footnote 2	If a subject prematurely withdraws from the study, all evaluations described under Visit 6/Week 12 must be performed.	**Subject may continue into open-label phase of study. If a subject is not continuing into open-label phase for any reason (see Section 4.1.2),** all evaluations described under Visit 6/Week 12 must be performed.	Clarification of process at Visit 6
6.1 – 6.2 Study Procedures at Visits 3 – 14	Record AEs	Record AEs **and Tolerability Assessments**	Changed at all post-Baseline Visits at request of FDA
6.1.1 Screening Visit	**Using the Interactive Web Response system (IWRS),** assign the subject a . . .	Assign the subject a . . .	Screening number will not be assigned by IWRS

Section	Revision		Rationale
	Old Text	**New Text**	
	Inserted	• **Collect blood and urine samples for clinical laboratory tests . . .**	Lab tests moved from Baseline to Screening Visit
6.1.2 Baseline Visit, Visit 1	• **Confirm eligibility**	none	Deleted repetition
	• **Collect blood and urine samples for clinical laboratory tests . . .**	deleted	Lab tests moved from Baseline to Screening Visit
6.1.3 Visit 2, Week 1	Inserted	• **Dispense 1 kit (2 canisters) of study drug**	Correction
6.1.4. Visit 3, Week 3	inserted	• **Collect blood and urine samples for clinical . . .**	Added per FDA request
	• **Confirm that subject continues to use the drug product and only provided cleanser correctly**	Deleted	Redundant
6.1.7. Visit 6, Week 12	End of Double-Blind or Early Termination	End of Double-Blind or **Continuation in Open Label /** Early Termination	Title changed for clarity
6.2 Part 2 – Open-label Table 2	Footnote inserted	Footnote 3 - **Home pregnancy tests will be dispensed to all female subjects at risk of becoming pregnant and will be performed whenever there is a suspicion of pregnancy (e.g., a missed period)**	Added at request of FDA
	Inserted	"**X**" for Tolerability Assessment at all post-Baseline visits	Added at request of FDA
	Inserted	"**X**" for Blood and urine samples at Week 28	Added at request of FDA
6.2.1 Visit 7 – Week 16	Dispense **1** kits (**2** canisters) of FMX-101, 4% minocycline foam if required	Dispense **2** kits (**4** canisters) of FMX-101, 4% minocycline foam if required	Correction
6.2.2 Visit 9, Week 28	inserted	• **At Visit 9 (Week 28) only – Collect blood and urine . . .**	Added per FDA request
7.1.3.1 Part 1 – Double-blind	none	**After shaking the canister well** . . .	Added text to include instruction to shake
	. . .supplies will be dispensed at Baseline and Weeks 3, 6 and 9 . . .	. . . supplies will be dispensed at Baseline and Weeks **1**, 3, 6 and 9 . . .	Correction

Section	Revision		Rationale
	Old Text	**New Text**	
7.1.5 Labeling of Study Drug	none	**"Shake well before using"**	Added text to label about shaking
7.1.6 Storage of Drug	FMX-101, 4% and vehicle canisters must be stored at 20°C – 25°C . . .	FMX-101, 4% and vehicle canisters must be stored at **2°C – 8°C until being dispensed to the subjects. Subsequently, they must be stored at** 20°C – 25°C . . .	Inclusion of instruction that site must keep drug refrigerated until it is dispensed
7.2 Study Drug Accountability	Inserted	**In addition, the weight of each canister will be determined prior to being dispensed to the subjects and each canister that has been retrieved from the subject will be returned to the vendor to be weighed**	Added per FDA request
7.7 Prior and Concomitant Therapy	Inserted	**If a subject is taking anticoagulant therapy, the subject should be advised that they may require a downward adjustment of their anticoagulant dosage.**	Tetracyclines may decrease plasma prothrombin activity
7.8 Use of Contraception	• Hormonal methods o Oral contraceptives . . . birth control must be utilized in subjects using topical contraceptives)	• Hormonal methods o Oral contraceptives . . . birth control must be utilized in subjects using **oral** contraceptives)	Correction
8.1.1 IGA Table 3	See a) below	See b) below	Removal of quantitative description of non-inflammatory lesions

Section	Revision		Rationale
	Old Text	**New Text**	
8.1.2 Lesion counts	Facial lesion counts . . . Inflammatory lesions (pustules, papules, and nodular lesions) and noninflammatory lesions (open and closed comedones) will be counted **for each area** and recorded separately. **The totals of inflammatory and non-inflammatory lesions will be calculated from these regional lesion counts.** Lesion counts will be repeated at Weeks 3, 6, 9 and 12. **Totals do not need to be calculated at these visits**.	Facial lesion counts . . . **Total** inflammatory lesions (pustules, papules, and nodular lesions) and noninflammatory lesions (open and closed comedones) will be counted and recorded separately. Lesion counts will be repeated at Weeks 3, 6, 9 and 12.	Counting method modified and addressed in Data Management Plan
9.2 Medication History	A history of medication usage . . . medications in the last 3 months **(6 months for acne medications)** will be recorded.	A history of medication usage . . . medications in the last 3 months will be recorded.	Consistency with Section 6.1.1.
9.4 Vital Signs	Heart rate and blood pressure will be measured at all visits.	Heart rate and blood pressure will be measured at all **post-Baseline** visits.	Correction
9.8.1 Method of Determining Adverse Events	inserted	• **Developed unusual headaches or changes in vision**	Queried at each visit as per FDA request
9.8.3. Reporting Adverse Events	Any serious AEs . . . must be reported to the Sponsor within . . .	Any serious AEs . . . must be reported to the Sponsor **or designee** within . . .	Correction of omission
10.2 Determination of Sample Size	None	See text at c) below	Modified as per FDA suggestion
10.4.1 Primary Efficacy Endpoints	IGA **score at** Week 12 (where success is defined as **at least a 2-grade decrease from Baseline)**.	**Treatment Success (dichotomized as Yes/No) at** Week 12, where success is defined as **an IGA score of 0 or 1, and at least a 2-grade improvement (decrease) from Baseline.**	Modified as per FDA suggestion

Section	Revision		Rationale
	Old Text	**New Text**	
10.4.2. Secondary Efficacy Endpoints	• The absolute change from Baseline in the noninflammatory lesion count at Week 12 • The absolute change from Baseline in the inflammatory lesion count and IGA at the interim visit at Week 9 • **The absolute change from Baseline in the noninflammatory lesion count at Week 9** • The absolute change from Baseline in the inflammatory lesion count and IGA Treatment Success at the interim visit at Week 6 • **The absolute change from Baseline in the noninflammatory lesion count at Week 6**	• The absolute change from Baseline in the noninflammatory lesion count at Week 12 • The absolute change from Baseline in the inflammatory lesion count and IGA **Treatment Success** at the interim visit at Week 9 • The absolute change from Baseline in the inflammatory lesion count and IGA **Treatment Success** at the interim visit at Week 6	Modified as per FDA suggestion
10.4.3. Tertiary Efficacy Endpoints	• The percent change from Baseline in the inflammatory lesion count at Weeks 3, 6, 9 and 12 • **The percent change from Baseline in the noninflammatory lesion count at Weeks 3, 6, 9 and 12** • The absolute change from Baseline in the inflammatory and noninflammatory lesions, and **the dichotomized IGA score, (where success is defined as at least a 2-grade decrease from Baseline),** at Week 3 • The percent change from Baseline in the noninflammatory lesion count at Weeks 3, 6, 9 and 12	• The percent change from Baseline in the inflammatory lesion count at Weeks 3, 6, 9 and 12 • The absolute change from Baseline in the inflammatory and noninflammatory lesions, and the IGA **Treatment Success** at Week 3 • **The absolute change from Baseline in the noninflammatory lesion count at Weeks 3, 6, and 9** • The percent change from Baseline in the noninflammatory lesion count at Weeks 3, 6, 9 and 12	Modified as per FDA suggestion

Section	Revision		Rationale
	Old Text	**New Text**	
10.6.3 Efficacy Analysis	The co-primary endpoint of **at least a 2-grade improvement (decrease) from Baseline in the IGA score** at Week 12 will be analyzed . . . overall **IGA response rates** are less than 10% . . . on the difference in **IGA success** rates between FMX-101 4% and vehicle.	The co-primary endpoint of **IGA Treatment Success rate** at Week 12 will be analyzed . . . overall **IGA Treatment Success rate** is less than 10% . . . on the difference **in IGA Treatment Success** rates between FMX-101 4% and vehicle.	Modified as per FDA suggestion
	. . .Testing of secondary efficacy endpoints at an earlier timepoint for each type of lesion and IGA will be performed only if superiority (one-sided p<=0.025) is seen at the later timepoint.	. Testing of secondary efficacy endpoints at an earlier timepoint for each type of lesion and IGA **Treatment Success** will be performed only if superiority (one-sided p<=0.025) is seen at the later timepoint.	Modified as per FDA suggestion
11.1 Monitoring	Monitoring visits will **apply** place . . .	Monitoring visits will **take** place	Correction
	. . . Sponsor . . .	. . . Sponsor or **Sponsor's representative .** . .	Multiple corrections

a) Old Table 3 – IGA Scale

Table 3: IGA Scale for Acne Vulgaris

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions present; rare **(eg, <5)** non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some noninflammatory lesions are present; few **(eg, <10)** inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	**Many noninflammatory lesions**; multiple **(eg, between 25 and 40)** inflammatory lesions **present**; many papules/pustules; there may or may not be a few nodulocystic lesions
4	Severe	Inflammatory lesions predominate, many papules/pustules **(eg, between 40 and 75**); there may be a few nodulocystic lesions
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

b) New Table 3 – IGA Scale

Table 3: IGA Scale for Acne Vulgaris

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions may be present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink- red)
2	Mild	Some noninflammatory lesions are present, **with** few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	**Many noninflammatory 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
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

c) Inserted in Section 10.2

Another consideration for the sample size must be given to the secondary endpoint of noninflammatory lesions which will be compared to the vehicle for non-inferiority. The margin for non-inferiority will be 30% of the change from baseline to week 12. In a phase 2 study, change from baseline in noninflammatory lesions at week 9 was 22.8 for the vehicle group with a standard deviation of 18. Assuming approximately the same reduction at week 12, a 30% non-inferiority margin is about 6.8 lesions. The following table provides approximate sample sizes for alternate assumptions for 90% power to show non-inferiority.

Vehicle mean noninflammatory lesion reduction	Minocycline 4% foam mean noninflammatory lesion reduction	Sample sizes (vehicle, active)
CCI	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI

If Minocycline 4% foam has the same effect on noninflammatory lesions as vehicle, CCI subjects on vehicle and CCI on 4% foam will be needed for 90% power to show non-inferiority. If Minocycline 4% foam has a slightly less effect on noninflammatory lesions (CCI lesion reduction versus CCI in vehicle), there will be about 90% power to show non-inferiority.

16.2.2. Amendment 2, effective April 6, 2016

The following is the summary of the changes that were made to Protocol FX2014-05 Version 2 issued February 26, 2016.

Section	Revision		Rationale
	Old Text	**New Text**	
5.2 Exclusion Criteria	2. Dermatological condition of the face or facial hair (eg, beard, sideburns, mustache) that could interfere with the clinical evaluations	2. **Acne conglobata, acne fulminans, secondary acne (chloracne, drug induced acne) or any dermatological condition**.	Specific exclusions added for clarity
6. Study Procedures Table 1: Schedule of Procedures	Urine pregnancy test (females, only)	Urine pregnancy test (females **of childbearing potential** only)	Clarification
	Inserted	**"X"** for pregnancy tests to be performed at **Week 3, 6 and 9**	Modified per FDA
	Inserted	New line and "**X**" for Subject Satisfaction Questionnaire for Week 12	Procedure added
Footnote 3	. . . **This visit and** the procedures required at this visit can be combined with Screening. . .	. . . The procedures required at **these visits** can be combined . . .	Clarification

Section	Revision		Rationale
	Old Text	**New Text**	
Footnote 6	Home pregnancy tests will be dispensed to all female subjects at risk of becoming pregnant and will be performed whenever there is a suspicion of pregnancy (e.g., a missed period)	**Perform urine pregnancy test at indicated visits. Also dispense home urine pregnancy test at Week 12 if subject is continuing into open-label treatment**	Modified per FDA
6.1.2. Baseline Visit, Visit 1	. . . **This visit and** the procedures required at this visit can be combined with Screening. . .	. . . The procedures required at **this visit** can be combined with Screening . . .	Clarification
	Perform urine pregnancy test	Perform urine pregnancy test **in females of childbearing potential**	Clarification
6.1.4. Visit 3, Week 3; 6.1.5. Visit 4, Week 6; 6.1.6. Visit 5, Week 9	Inserted	**Perform urine pregnancy test in females of childbearing potential**	Modified per FDA
6.1.7. Visit 6, Week 12	Collect a urine sample from female subjects for a urine pregnancy test	**Perform urine pregnancy test in females of childbearing potential**	Clarification
	Inserted	• **Administer Subject Satisfaction Questionnaire**	Procedure added
	• If subject is continuing . . . dispense 1 kit (2 canisters) of FMX-101 . . .	• If subject is continuing . . . dispense **2 kits (4 canisters)** of FMX-101 .	Correction
6.2 Part 2 – Open-label Table 4: Schedule of Procedures	Inserted	"**X**" for pregnancy tests to be dispensed at Weeks 16, 22, 28, 34, 40 and 46.	Modified per FDA
	Inserted	New line and "**X**" for Subject Satisfaction Questionnaire for Week 52	Procedure added
Footnote 3	Home pregnancy tests will be dispensed to all female subjects at risk of becoming pregnant whenever . . .	Home pregnancy tests will be dispensed **at each visit** to all **female subjects of childbearing potential** and will be performed at least **monthly and** whenever . . . **Perform urine pregnancy test at Final Visit.**	Modified per FDA

Section	Revision		Rationale
	Old Text	**New Text**	
6.2.1. Visit 7, Week 16	Inserted	**Dispense Home pregnancy kit to all female subjects of childbearing potential**	Modified per FDA
6.2.2. Visits 8 – 12, Weeks 22 – 46	Inserted	**Dispense Home pregnancy kit to all female subjects of childbearing potential**	Modified per FDA
6.2.3. Visit 13, Final Visit – Week 52	Collect a urine sample from female subjects for a urine pregnancy test	**Perform urine pregnancy test in females of childbearing potential**	Clarification
	Inserted	• **Administer Subject Satisfaction Questionnaire**	Procedure added
7.1.3.1. Part 1 – Double-blind	After shaking . . . , a small amount of foam should be expressed . . . . additional amounts of foam should also be applied . . .approximately the same time each day preferably in the evening.	After shaking . . .a small amount of foam **(about 1/2 gram or a cherry-sized amount)** should be expressed . . . additional amounts **(up to a total of 4g)** of foam should also be applied . . .the same time each day preferably in the evening **at bedtime**.	Clarification of amounts and timing
8.3. Subject Satisfaction Questionnaire	Inserted	**A satisfaction questionnaire will be administered at Visit 6, Week 12 and Visit 13, Week 52 (see Section 16.1, Appendix 1).**	Procedure added
9.6. Clinical Laboratory Tests	Serum chemistry, hematology and urinalysis will be evaluated at Baseline, Week 12 and Final Visit.	Serum chemistry, hematology and urinalysis will be evaluated at Baseline, Week 12/ Final Visit **of the double-blind phase of the Study, and at Week 28 and Week 52/Final Visit of the open-label phase of the Study**.	Modified per FDA

Section	Revision		Rationale
	Old Text	**New Text**	
9.6.1. Urine Pregnancy Test	A urine sample will be collected from all female subjects for a urine pregnancy test at Baseline, Week 12 and Final Visit or when a subject prematurely withdraws from the study.	A urine **pregnancy test will be performed on all females of childbearing potential at Baseline, Week 3, Week 6, Week 9 and Week 12 of the double-blind phase of the Study** and Final Visit or when a subject prematurely withdraws from the study. **Home pregnancy kits will be provided at each visit to all female subjects of childbearing potential in the open-label phase of the Study and are to be used at least monthly and if a pregnancy is suspected between visits (e.g., if a subject misses a period). A urine pregnancy test will be performed at Week 52/ Final Visit.**	Modified per FDA
9.7.1. Tolerability	. . pigmentation . . .	. . .**hyper**pigmentation . . .	Correction
9.8.4. Adverse Event Follow-up	Adverse events that are ongoing when a subject withdraws from or completes the study will be followed until resolution or stabilization (in the opinion of the Investigator), or for 30 days, whichever is shorter.	Adverse events, **and tolerability signs and symptoms greater than zero (0),** that are ongoing when a subject withdraws from or completes the study will be followed until resolution or stabilization (in the opinion of the Investigator), or for 30 days, whichever is shorter.	Modified as per FDA suggestion
9.8.4.1. Pregnancy reporting	A urine pregnancy test will be performed . . . at Baseline and Week 12/Final Visit of the double-blind phase of the Study or when a subject prematurely withdraws . . .	A urine pregnancy test will be performed . . .at Baseline, **Week 3, Week 6, Week 9** and Week 12/Final Visit of the double-blind phase of the Study or when a subject prematurely withdraws . . .	Modified as per FDA suggestion

Section	Revision		Rationale
	Old Text	**New Text**	
	Home pregnancy kits will be provided to all female subjects at risk of becoming pregnant and are to be used if a pregnancy is suspected between visits (e.g., if a subject misses a period).	Home pregnancy kits will be provided to all female subjects **of childbearing potential in the open-label phase of the Study** and are to be used **at least monthly and** if a pregnancy is suspected between visits (e.g., if a subject misses a period). A urine pregnancy test will be performed at Final Visit.	
10.3 Analysis Populations	• Have not been compliant with the dosing regimen (ie, subjects missed more than 5 consecutive days of dosing and took less than 80% of expected doses)	• Have not, **in the opinion of the investigator, been compliant with the treatment regimen (e.g. reported frequent missed doses)**	Modify definition of Per Protocol Population
10.6.3 Efficacy Analysis	Non-inferiority margin is defined as 40% of the noninflammatory lesion reduction in the vehicle group at Week 12	Non-inferiority margin is defined as **30%** of the noninflammatory lesion reduction in the vehicle group at Week 12	Correction
16.1. Appendix 1 – Subjects Satisfaction Questionnaire	Inserted	See **Appendix 1** (p.52)	Procedure added

16.2.3. Amendment 3, effective October 14, 2016

The following is the summary of the changes that were made to Protocol FX2014-05 Version 3 issued April 6, 2016.

Section	Revision		Rationale
	Old Text	**New Text**	
1. Synopsis	Subjects who successfully complete the 12-week double blind portion of the study will be offered . . .	Subjects who successfully complete the 12-week double blind portion of the study **may** be offered . . .	Not all subjects will be eligible to continue
1.7.2. Part 2 – Open-label 4.1.2. Part 2 – Open-label	At the Week 12 Visit, subjects may be invited to continue into the open-label part of this study . . .	At the Week 12 Visit, subjects **whose IGA score has not worsened** may be invited to continue into the open-label part of this study . . .	Minimize risk of prolonging ineffective treatment
1.7.2. Part 2 – Open-label 4.1.2. Part 2 – Open-label	Subjects may be discontinued from the study at any time if their disease becomes refractory . . .	Subjects may be discontinued from the study **after 12 weeks** if their disease becomes refractory . . .	Avoid prolongation of ineffective therapy
6.1.2.Baseline Visit 1 6.1.3 Visit 2, Week 1 6.1.4 Visit 3, Week 3 6.1.5 Visit 4, Week 6 6.1.6 Visit 5, Week 9 6.1.7 Visit 6, Week 12 End of Double-Blind or Continuation in Open Label / Early Termination	· Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight	· Schedule/confirm the next study visit and remind subject to avoid overexposure **to natural or artificial sunlight**	Remind subjects in double-blind phase of study to avoid exposure overexposure to natural and artificial sunlight
6.2.1 Visit 7 6.2.2 Visits 8 - 12	· Schedule/confirm the next study visit	· Schedule/confirm the next study visit **and remind subject to avoid overexposure to natural or artificial sunlight**	Remind subjects in open-label phase of study to continue to avoid overexposure to natural and artificial sunlight.

Section	Revision		Rationale
	Old Text	**New Text**	
7.7 Prior and Concomitant Therapy	Inserted	**Benzoyl peroxide (e.g., Pro-Activ, Clearasil) can inactivate minocycline and may thus decrease the effectiveness of FMX-101 if the two products are applied at the same time. Treated areas should be washed between applications of FMX-101 and products containing benzoyl peroxide. Preferably, the products should be applied no less than 8 hours apart.**	Minimize potential for drug interaction
9.8.1 Method of Determining Adverse Events	All questions should be of a general nature and should not suggest symptoms.	**With the exception of the last item above,** all questions should be of a general nature and should not suggest symptoms.	Reminder that these AEs should be actively questioned.

CLINICAL STUDY PROTOCOL

Title:	A Randomized, Double-Blind Study to Compare the Efficacy, Safety and Long-Term Safety of Topical Administration of FMX-101 for 1 Year in the Treatment of Moderate-to-Severe Acne Vulgaris, Study FX2014-05
Development Phase:	3
Project Number:	FMX-101
Study drug(s):	FMX-101, minocycline foam 4%; matching vehicle foam
Indication:	Acne vulgaris
Authors:	PPD
Protocol Number:	FX2014-05
Version	3
Date of Protocol:	April 6, 2016
Supersedes	Version 2 of February 26, 2016

Title: A Randomized, Double-Blind Study to Compare the Efficacy, Safety and Long-Term Safety of Topical Administration of FMX-101 for 1 Year in the Treatment of Moderate-to-Severe Acne Vulgaris, Study FX2014-05

CONFIDENTIAL

PROJECT NUMBER: FMX-101

	Name/Title	Signature	Date
CLINICAL RESEARCH:	PPD	PPD	4/6/16
REGULATORY AFFAIRS:	PPD	PPD	4/6/16
		PPD PPD	

1. SYNOPSIS

This is a Phase 3 study to evaluate the efficacy, safety and long-term safety of the topical administration of FMX-101, 4% minocycline foam for the treatment of moderate-to-severe acne vulgaris. The first 12 weeks of the study involves randomized, double-blind treatment with active FMX-101, 4% or matching vehicle. Subjects who successfully complete the 12-week double blind portion of the study will be offered the opportunity to continue in the trial for up to an additional 40 weeks (for a total of 1 year) and receive open-label treatment with FMX-101, 4%.

1.1. Investigational Product, Dosage, and Mode of Administration

The investigational product is FMX-101, minocycline foam 4%. FMX-101 4% will be applied topically daily for the 12-week treatment duration of the study.

1.2. Active Ingredient

The active ingredient is minocycline HCl.

1.3. Reference Product, Dosage, and Mode of Administration

The reference product is vehicle foam. Vehicle foam will be applied topically daily for the 12-week treatment duration of the study.

1.4. Study Centers

Approximately 30 study centers will participate in this study.

1.5. Study Period

Estimated date first subject enrolled: April 2016

Estimated date last subject completed: August 2017

1.6. Study Objectives

The objectives of this study are:

- To evaluate the efficacy in the treatment of acne compared to vehicle of topical FMX-101, 4% administered daily for 12 weeks
- To evaluate the safety compared to vehicle of topical FMX-101, 4% administered daily for 12 weeks
- To evaluate the long-term safety of topical FMX-101, 4% administered daily for up to 40 additional weeks

1.7. Methodology

The study will have 2 parts. The first will involve 12 weeks of double-blind treatment with FMX-101, 4% or vehicle foam. The second will involve up to 40 additional weeks of open-label treatment with FMX-101, 4% of subjects who complete the first part of the study.

1.7.1. Part 1 – Double-blind Period

This is a randomized, multicenter, double-blind, vehicle-controlled, 2-arm study to evaluate the safety and efficacy over 12 weeks of FMX-101 minocycline foam, 4%, compared to vehicle, in the treatment of subjects with moderate to severe facial acne vulgaris.

Qualified subjects will be randomized to receive 1 of the following 2 treatments:

- FMX-101, 4% minocycline foam
- Vehicle foam

Subjects with qualifying lesion counts (Section 8.1.2) and Investigator's Global Assessments (IGA, Section 8.1.1) of acne severity scores and will be assigned to 1 of 2 treatments according to the randomization schedule. Subjects will apply the assigned study drug topically once daily for 12 weeks as directed. Subjects will be advised to apply the study drug at approximately the same time each day, preferably in the evening at bedtime. Both the Investigator and subject will be blinded to the study drug identity.

Subjects will return for visits at Weeks 1, 3, 6, 9, and 12. At the discretion of the clinic staff, for the convenience of subjects or clinic staff, visits can be scheduled to occur 3 days before or after the nominal schedule date for the Weeks 1, 3 and 6 visits and 7 days before or after for the Weeks 9 and 12 visits. Efficacy evaluations (acne lesion counts and IGAs will be performed at Weeks 3, 6, 9, and 12 during the study. Other assessments will be performed as described in Section 9.

1.7.2. Part 2 – Open-label

At the Week 12 Visit, subjects may be invited to continue into the open-label part of this study for an additional 9 months of treatment. Subjects will be enrolled in this phase of the study until a total of approximately 400 subjects from Studies FX2014-04 and FX2014-05 have elected to continue in the open-label portion of their respective study. Subjects who elect to continue into the open-label part of this study will receive supplies of active FMX-101, 4% minocycline foam.

Treatment during this part of the study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment of some or all areas if there is clinical improvement or resolution of the acne in those areas. Even if the treatment is partially or completely temporarily suspended, the subject will be continued in the study and will make all scheduled clinic visits. If at any time the acne recurs or worsens, treatment of the affected areas may be resumed.

Subjects may be discontinued from the study at any time if their disease becomes refractory or they become intolerant of the product.

1.8. Number of Subjects

The planned enrollment is 450 subjects. Subjects will be randomized to active or vehicle in a 2:1 ratio. Approximately 300 and 150 subjects will be assigned to the FMX-101, 4% or vehicle treatment groups, respectively.

1.9. Diagnosis and Main Criteria for Inclusion

Subjects are to be at least 9 years of age.

Eligible subjects are to have a diagnosis of facial acne vulgaris characterized by (subjects are permitted to also have acne on other parts of the body):

- 20 to 50 inflammatory lesions (papules, pustules, and nodules)
- 25 to 100 noninflammatory lesions (open and closed comedones)
- No more than 2 nodules on the face
- Investigator's Global Assessment (IGA) score of moderate (3) to severe (4)

1.10. Criteria for Evaluation

1.10.1. Efficacy

The efficacy assessments will include the IGA and lesion counts at Baseline and Weeks 3, 6, 9 and 12.

1.10.2. Safety

The safety assessments in this study are physical examinations, vital signs, assessment of the skin at application site(s), adverse events (volunteered, observed, and elicited by general questioning in a non-suggestive manner), and clinical laboratory test results.

1.11. Statistical Methods

Efficacy analyses will be conducted on the Intent-to-Treat (ITT) population, using the last-observation-carried-forward (LOCF) approach to impute missing values. Supportive efficacy analyses will also be conducted on the Per Protocol (PP) population, with no imputation for missing values. The co-primary efficacy endpoints are the absolute change from Baseline in the inflammatory lesion count at Week 12 IGA Treatment Success (dichotomized as Yes/No) at Week 12, where success is defined as an IGA score of 0 or 1, and at least a 2-grade decrease from Baseline. FMX-101 4% will be tested against vehicle at the two-sided 0.05 level of significance without adjustment for multiplicity. The absolute change from Baseline in inflammatory lesions at Week 12 will be analyzed using an Analysis of Covariance (ANCOVA) model with main effect treatment and investigational site as a covariate. The IGA Treatment Success rates will be compared between the treatment groups using a Cochran–Mantel–Haenszel (CMH) test stratified for investigational site.

No statistical tests will be performed for any of the safety assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
CFR	Code of Federal Regulations
CRF	Case report form
eCRF	Electronic case report form
EKG	Electrocardiogram
FDA	Food & Drug Administration
GCP	Good Clinical Practice
HEENT	Head, eyes, ears, nose, and throat
ICF	Informed consent form
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
IWRS	Interactive Web Response System (IWRS)
LOCF	Last-observation-carried-forward
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OC	Observed-Cases
P. acnes	Propionibacterium acnes
PP	Per protocol
TEAE	Treatment-emergent adverse event
SAE	Serious adverse event
SOC	System organ class

STUDY ADMINISTRATIVE STRUCTURE

Name	Affiliation / Address / Telephone Number	Responsibility
Foamix Pharmaceuticals, Inc	520 U.S. Highway 22, Suite 305 Bridgewater, NJ 08807	Sponsor
TKL Research, Inc.	365 West Passaic Street, Suite 550 Rochelle Park, NJ 07662	CRO
PPD	TKL Research, Inc.	PPD
PPD	TKL Research, Inc.	PPD

2. INTRODUCTION

Acne vulgaris is a common disease of both males and females, usually manifesting initially during adolescence. The primary pathologic events are initiated in the pilo-sebaceous 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 pilo-sebaceous follicle and increased sebum produced in the gland, a blockage of the duct results in the inapparent clinical lesion of the microcomedone. Continued blockage, colonization of the follicle by Propionibacterium acnes (P. 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]

FMX-101, 4% is a minocycline containing topical foam being developed as a treatment for acne vulgaris. Antibiotics, especially erythromycin, minocycline, and doxycycline, have been prescribed as acne treatments for many years. These antibiotics effectively control the signs of inflammatory acne while patients continue to use them. Nonclinical studies have demonstrated that FMX-101, 4% exhibits favorable characteristics.

Foamix has conducted 2 Phase 1 and 1 Phase 2 study of FMX-101, 4% to assess its safety and tolerability. FMX-101, 4% has been shown to be effective and well tolerated at the 4% dose that is being utilized in this study. The Investigator's Brochure should be consulted for summaries of the results of these studies.

This Phase 3 study (Study FX2014-05) will assess the efficacy, safety and long-term safety of FMX-101, 4% for the treatment of moderate to severe facial acne vulgaris.

3. STUDY OBJECTIVES

The objectives of this study are:

- To evaluate the efficacy in the treatment of acne compared to vehicle of topical FMX-101, 4% administered daily for 12 weeks
- To evaluate the safety compared to vehicle of topical FMX-101, 4% administered daily for 12 weeks
- To evaluate the long-term safety of topical FMX-101, 4% administered daily for up to an additional 40 weeks

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The one-year study will have 2 parts. The first 12 weeks will be double-blind treatment with FMX-101, 4% or vehicle foam. The remaining 40 weeks will involve open-label treatment with FMX-101, 4% by any subjects who complete the first part of the study.

4.1.1. Part 1 – Double-blind

This is a randomized, multicenter, double-blind, vehicle-controlled, 2-arm study to evaluate the safety and efficacy over 12 weeks of FMX-101 minocycline foam, 4%, compared to vehicle, in the treatment of subjects with moderate to severe facial acne vulgaris.

Qualified subjects will be randomized to receive 1 of the following 2 treatments:

- FMX-101, 4% minocycline foam
- Vehicle foam

Subjects with qualifying lesion counts (Section 8.1.2) and Investigator's Global Assessments (IGA, Section 8.1.1) of acne severity scores and will be assigned to 1 of 2 treatments according to the randomization schedule. Subjects will apply the assigned study drug topically once daily for 12 weeks as directed. Subjects will be advised to apply the study drug at approximately the same time each day, preferably in the evening before bedtime. Both the Investigator and subject will be blinded to the study drug identity.

Subjects will return for visits at Weeks 1, 3, 6, 9, and 12. Efficacy evaluations (acne lesion counts and IGAs will be performed at Weeks 3, 6, 9, and 12 during the study. Other assessments will be performed as described in Sections 8.2 and 9.

4.1.2. Part 2 – Open-label

At the Week 12 Visit, subjects may be invited to continue into the open-label part of this study for an additional 9 months of treatment. Subjects will be enrolled in this phase of the study until a total of approximately 400 subjects from Studies FX2014-04 and FX2014-05 have elected to continue in the open-label portion of their respective study. Subjects who elect to continue into the open-label part of this study will receive supplies of active FMX-101, 4% minocycline foam.

Treatment during this part of the study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment of some or all areas if there is clinical improvement or resolution of the acne in those areas. Even if the treatment is partially or completely temporarily suspended, the subject will continue in the study and make all scheduled clinic visits. If at any time the acne recurs or worsens, treatment of the affected areas may be resumed.

Subjects may be discontinued from the study at any time if their disease becomes refractory or they become intolerant of the product.

4.2. Rationale for Study Design and Dose Selection

A randomized, multicenter, double-blind, vehicle-controlled study design has been selected in order to assess the efficacy of the study drug in accordance with the FDA Guidance.[2] The subjects will be selected according to predefined entry criteria. The study will have a 12-week treatment duration.

FMX-101 foam, 4% is a novel minocycline formulation that has been shown to have efficacy in once daily use in a Phase 2 study. The once daily dosing regimen is appropriate given the pharmacokinetic characteristics of FMX-101, 4%.

Because of the mode of action of tetracycline drugs, the primary efficacy endpoints will be the effect on inflammatory lesion count and IGA (Section 8.1.1). The effect on noninflammatory lesions will be the most important secondary endpoint.

The extension of the study for an additional 40 weeks is necessary to obtain safety information about the long-term use of FMX-101, 4% to treat acne, which is a chronic condition. The design of the study is expected to provide sufficient safety information to fulfill the ICH E1 guideline.

5. STUDY POPULATION

The planned enrollment is 450 subjects. Subjects will be randomized to active or vehicle in a 2:1 ratio. Approximately 300 and 150 subjects will be assigned to the FMX-101, 4% or vehicle treatment groups, respectively.

5.1. Inclusion Criteria

A male or female subject will be considered eligible for participation in the study if all of the following inclusion criteria are satisfied prior to randomization:

1. Has completed and signed an appropriately administered Informed Consent Form (ICF) prior to any study-related procedures. Subjects less than 18 years of age (or as required by state law) must sign an Assent Form for the study and a parent or legal guardian must sign the ICF.
2. Is 9 years of age or greater,
3. Has facial acne vulgaris with:
   - 20 to 50 inflammatory lesions (papules, pustules, and nodules)
   - 25 to 100 noninflammatory lesions (open and closed comedones)
   - No more than 2 nodules on the face
   - IGA score of moderate (3) to severe (4)
4. If women of child-bearing potential, have a negative urine pregnancy test
5. For women of child-bearing potential at risk of becoming pregnant, agree to an effective method of contraception (Sections 7.7 and 7.8)
6. Willing to use only the supplied non-medicated cleanser CCI and to refrain from use of any other acne medication, medicated cleanser, excessive sun exposure, and tanning booths for the duration of the study

5.2. Exclusion Criteria

Subjects who have any of the following will be excluded from the study:

1. Female who is pregnant or lactating, or is planning a pregnancy during the study
2. Acne conglobata, acne fulminans, secondary acne (chloracne, drug induced acne) or any dermatological condition of the face or facial hair (eg, beard, sideburns, mustache) that could interfere with the clinical evaluations

3. Sunburn on the face
4. Severe systemic disease, which might interfere with the conduct of the study or the interpretation of the results.
5. Abnormal baseline laboratory values that are considered clinically significant.
6. Currently participating, or has participated within 30 days prior to this study, in an investigational drug or device study
7. Inability to fully comply with the study requirements

Subjects who have a history of any of the following will be excluded:

8. Allergy to tetracycline-class antibiotics or to any ingredient in the study drug
9. Pseudomembranous colitis or antibiotic-associated colitis
10. Hepatitis or liver damage or renal impairment
11. Known or suspected premalignant or malignant disease (excluding successfully treated skin cancers)
12. Subjects who have used the following medications (topical refers only to the facial area) will not be eligible:

    Within 1 week prior to randomization:

    - Medicated facial cleansers
    - Topical acne treatments (other than those listed below)

    Within 4 weeks prior to randomization:

    - Topical retinoids
    - Topical anti-inflammatories and corticosteroids
    - Systemic antibiotics
    - Systemic acne treatments

    Within 12 weeks prior to randomization:

    - Systemic retinoids
    - Systemic corticosteroids
13. Drug addiction or alcohol abuse (within the last 2 years).
14. Current or significant past history of depression.

6. STUDY PROCEDURES

Potential subjects will be assessed for eligibility at Screening. During this visit, the purpose, timing, procedures, and risks of the study will be explained to the subject, including requirements for enrollment and participation in the study, medication restrictions during the study, and requirements for washout of certain medications that the subject may already be taking.

The eligible subject who is willing to participate in the study will then sign an appropriately administered Informed Consent Form (ICF) prior to any study-related procedures. Subjects less than 18 years of age (or per state law) must sign an Assent Form for the study and a parent or legal guardian must sign the ICF.

Procedures at the Screening Visit will include obtaining blood and urine samples for clinical laboratory tests. These results must be no more than 30 days old at the time of Baseline Visit randomization.

If a subject, who has agreed to participate in the study and signed the ICF or Assent Form, is currently undergoing acne therapy identified in Exclusion Criterion 12, they must first enter a washout period, before beginning the Screening procedures.

A summary of study assessments and the time point at which they will be performed during the study is presented in Table 1. If a subject prematurely withdraws from the study before the Week 12 Visit, the subject should return to the study site for a withdrawal visit, during which all evaluations described under Visit 6/Week 12 must be performed.

See

Table 2 and Section 6.2 for descriptions of the procedures required during the open-label part of the study.

Table 1: Schedule of Procedures - Study FX2014-05 – Part 1

Assessment	Screening [1]	Baseline [1]	Visits				"Final" Visit [2]
Visit		**1**	**2**	**3**	**4**	**5**	**6**
Week			**1**	**3**	**6**	**9**	**12**
Informed Consent/Assent	X						
Demographic Data	X						
Assign identification number	X						
Medical/Surgical/Medication (prior/concomitant) History	X						
Inclusion/Exclusion criteria	X	X					
Physical Exam, height, weight [3,4]		X					X
Blood Pressure/heart rate [5]		X	X	X	X	X	X
Blood and urine samples for clinical laboratory tests	X			X			X
Urine pregnancy test (females of childbearing potential only)[6]		X		X	X	X	X
Investigator's Global Assessment	X	X		X	X	X	X
Lesion Count	X	X		X	X	X	X
Photography		X			X		X
Subject Satisfaction Questionnaire							X
Randomization		X					
Concomitant Medication		X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Tolerability Assessments			X	X	X	X	X
Perform drug accountability			X	X	X	X	X
Collect empty canisters			X	X	X	X	X
Dispense Study Drug		X	X	X	X	X	X[7]
Schedule/Confirm Next Visit	X	X	X	X	X	X	X

[1] The duration of Screening is variable but if there are medications to be discontinued it can not be less than the time indicated in Exclusion Criterion 12. The procedures required at these visits can be combined. However, **drug should not be dispensed until all inclusion and exclusion criteria are met.**

[2] Subject may continue into open-label phase of study. If a subject is not continuing into open-label phase for any reason (see Section 4.1.2, all evaluations described under Visit 6/Week 12 must be performed.

[3] Height to be measured only at Baseline

[4] Including 12-lead EKG at Screening in subjects over 39 years of age

[5] Measure blood pressure and heart rate after the subject has been sitting for at least 5 minutes at rest

[6] Perform urine pregnancy test at indicated visits. Also dispense home urine pregnancy test at Week 12 if subject is continuing into open-label treatment

[7] If subject is continuing into open-label treatment phase, dispense appropriate Study Drug Kit

6.1. Part 1 – Double-Blind

6.1.1. Screening Visit

- Obtain a signed and dated, written Informed Consent Form (ICF) prior to any study-related procedures; subjects less than 18 years of age (or as required by state law) must sign an Assent Form for the study and a parent or legal guardian must sign the ICF. (Subjects must be at least 9 years of age at the time of assent/consent)
- Obtain demographic data
- Assign the subject a unique subject identification number
- Obtain medical history
- Obtain surgical history
- Obtain history of prior and concomitant medication usage (including previous use of acne medications); record start and stop dates of any medications used in the last 3 months
- Perform IGA (Section 8.1.1)
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions (Section 8.1.2)
- Record regions beyond face affected by acne
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 9.6)
- If subject wears make-up, remind the subject not to wear any make-up at future visits.
- Record AEs
- Schedule/confirm the next study visit. Remind subject to avoid sun overexposure.

6.1.2. Baseline Visit, Visit 1

The procedures required at this visit can be combined with Screening. However, drug should not be dispensed until all inclusion and exclusion criteria are met.

- Confirm/reconfirm eligibility according to the inclusion/exclusion criteria and
    - Perform IGA
    - Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Perform photography (Section 8.2)
- Measure blood pressure and heart rate (Section 9.4)
- Perform physical examination including height and weight (Section 9.5)
- Perform 12-lead EKG if subject is over 39 years of age

- Perform urine pregnancy test in females of childbearing potential
- Randomize the subject using the IWRS system, when all criteria have been met
- Record concomitant medications
- Record AEs
- Dispense 1 kit (2 canisters) of study drug
- Dispense cleanser [redacted]
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight

6.1.3. Visit 2, Week 1

- Measure blood pressure and heart rate
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use properly; confirm that only provided cleanser is being used.
- Collect previously dispensed study drug canister(s) if applicable
- Dispense 1 kit (2 canisters) of study drug
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight

6.1.4. Visit 3, Week 3

- Measure blood pressure and heart rate
- Perform urine pregnancy test in females of childbearing potential
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 9.6)
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use properly; confirm that only provided cleanser is being used.
- Collect previously dispensed study drug canister(s) if applicable
- Dispense 1 kit (2 canisters) of study drug
- Determine if additional drug or cleanser needs to be dispensed.

- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight

6.1.5. Visit 4, Week 6

- Measure blood pressure and heart rate
- Perform urine pregnancy test in females of childbearing potential
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Perform photography
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use properly; confirm that only provided cleanser is being used.
- Collect previously dispensed study drug canister(s) if applicable
- Dispense 1 kit (2 canisters) of study drug
- Determine if additional drug or cleanser needs to be dispensed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight

6.1.6. Visit 5, Week 9

- Measure blood pressure and heart rate
- Perform urine pregnancy test in females of childbearing potential
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use properly; confirm that only provided cleanser is being used.
- Collect previously dispensed study drug canister(s) if applicable
- Dispense 1 kit (2 canisters) of study drug
- Determine if additional drug or cleanser needs to be dispensed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight

6.1.7. Visit 6, Week 12 End of Double-Blind or Continuation in Open Label / Early Termination

- Perform physical examination including weight
- Measure blood pressure and heart rate
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory
- Perform urine pregnancy test in females of childbearing potential
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Perform photography
- Administer Subject Satisfaction Questionnaire
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use properly; confirm that only provided cleanser is being used.
- Collect previously dispensed study drug canister(s)
- If subject is continuing into the open-label phase of the study (see Section 4.1.2), dispense 2 kit (4 canisters) of FMX-101, 4% minocycline foam
    - If subjects facial acne is “clear” or “almost clear,” consider withholding treatment with FMX-101, 4% at this time but continue subject in study and schedule next visit.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight

6.2. Part 2 – Open-label

A summary of study assessments and the time point at which they will be performed during the Part 2 of this study is presented in

Table 2. If a subject prematurely withdraws from the study, the subject should return to the study site at which time all evaluations described under Final Visit 13/Week 52 must be performed.

Table 2: Schedule of Procedures - Study FX2014-05 – Part 2

Assessment	Visits						Final Visit [1]
Visit	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Week	**16**	**22**	**28**	**34**	**40**	**46**	**52**
Physical Exam, weight,							X
Blood Pressure/heart rate [2]	X	X	X	X	X	X	X
Blood and urine samples for clinical laboratory tests			X				X
Urine pregnancy test (females of childbearing potential only)[3]	X	X	X	X	X	X	X
Investigator's Global Assessment	X	X	X	X	X	X	X
Lesion Count	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Tolerability Assessment	X	X	X	X	X	X	X
Subject Satisfaction Questionnaire							X
Perform drug accountability	X	X	X	X	X	X	X
Collect empty canisters	X	X	X	X	X	X	X
Dispense Study Drug	X	X	X	X	X	X	
Schedule/Confirm Next Visit	X	X	X	X	X	X	

[1] If a subject prematurely withdraws from the study, all evaluations described under Final Visit 13/Week 52 must be performed.
[2] Measure blood pressure and heart rate after the subject has been sitting for at least 5 minutes at rest
[3] Home pregnancy tests will be dispensed at each visit to all female subjects of a childbearing potential and will be performed at least monthly and whenever there is a suspicion of pregnancy (e.g., a missed period). Perform urine pregnancy test at Final visit.

6.2.1. Visit 7 - Week 16

- Measure blood pressure and heart rate
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Assess product use to confirm that subject continues to use study drug properly
- Collect empty study drug canister(s)
- Dispense 2 kits (4 canisters) of FMX-101, 4% minocycline foam if required
- Dispense Home pregnancy kit to all female subjects of childbearing potential
- Schedule/confirm the next study visit
    - If subjects facial acne is "clear" or "almost clear," consider withholding treatment with FMX-101, 4% at this time but continue subject in study and schedule next visit.
    - If treatment has been interrupted, consider restarting treatment if clinically indicated

6.2.2. Visits 8, 9, 10, 11 and 12 – Weeks 22, 28, 34, 40 and 46

- Measure blood pressure and heart rate
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Record concomitant medications
- Record AEs and Tolerability Assessment
- At **Visit 9 (Week 28) only** - Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 9.6)
- Assess product use to confirm that subject continues to use study drug properly
- Collect empty study drug canister(s)
- Dispense 2 kits (4 canisters) of FMX-101, 4% minocycline foam if required
- Dispense Home pregnancy kit to all female subjects of childbearing potential
- Schedule/confirm the next study visit
    - If subjects facial acne is "clear" or "almost clear," consider withholding treatment with FMX-101, 4% at this time but continue subject in study and schedule next visit.

- If treatment has been interrupted, consider restarting treatment if clinically indicated

6.2.3. Visit 13, Final Visit – Week 52

- Measure blood pressure and heart rate
- Perform physical examination including weight
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory
- Perform urine pregnancy test in females of childbearing potential
- Perform IGA
- Perform facial lesion count of inflammatory, noninflammatory, and nodular lesions
- Record concomitant medications
- Record AEs and Tolerability Assessment
- Administer Subject Satisfaction Questionnaire
- Collect previously dispensed study drug canister(s)

7. STUDY TREATMENTS

FMX-101, 4% and vehicle will be supplied as identical canisters. All study drug will be stored, inventoried, reconciled, and destroyed according to US regulations.

7.1. Treatments Administered

The description of study drug kits and treatments is shown below.

7.1.1. Part 1 (double-blind) – Weeks 1 to 12

Dosage form description	Active kit: FMX-101 minocycline foam, 4%; Vehicle kit: Matching vehicle foam
Package description	Active kit: 2 canisters of FMX-101, 4% dispensed as foam when actuator is depressed Vehicle kit: 2 canisters dispensing vehicle foam when actuator is depressed
Daily dose	Approximately 0.5 gm of FMX-101, 4% (containing 40 mg minocycline per gram of foam; 0 mg for vehicle subjects); applied to face topically each day. Additional drug product may be applied to other acne-affected areas
Cumulative maximal dose	Approximately 1,680 mg of minocycline (0 mg for vehicle subjects) assuming application of 0.5 gm of foam daily to the face for 84 days. Maximum total amount of drug dispensed contains 14 gm of minocycline.
Dispensing	1 Kit (2 canisters) dispensed at Baseline and Weeks 1, 3, 6, and 9. Total of 5 kits (10 canisters) dispensed to the subject for the study.

7.1.2. Part 2 (open-label) – Weeks 13 to 52

Dosage form description	FMX-101 minocycline foam, 4%;
Package description	Active kit: 2 canisters of FMX-101, 4% dispensed as foam when actuator is depressed
Daily dose	Approximately 0.5 gm of FMX-101, 4% (containing 40 mg minocycline per gram of foam) applied to face topically each day. Additional drug product may be applied to other acne-affected areas
Cumulative maximal dose	Up to approximately 5,600 mg of minocycline assuming application of 0.5 gm of FMX-101 foam daily to the face for 280 days. Maximum total amount of drug dispensed contains 39.2 gm of minocycline.
Dispensing	Up to 2 Kits (4 canisters) dispensed at Weeks 12, 16, 22, 28, 34, 40 and 46 depending on rate of usage. Up to a total of 14 kits (28 canisters) dispensed to the subject for the study.

7.1.3. Dosing Instructions

7.1.3.1. Part 1 – Double-blind

The dosing regimen will be the same for both treatment groups.

After shaking the canister well, a small amount of foam (about 1/2 gram or a cherry-sized amount) should be expressed from the canister onto the fingertips of the hand and then rubbed into acne-affected parts of the face. This should be repeated as needed until all acne-affected parts of the face are treated. If acne is present on other parts of the subject's body (neck, shoulders, arms, back or chest) additional amounts (up to a total of 4g) of foam should also be applied to these areas. The foam should be applied at approximately the same time each day preferably in the evening at bedtime. The subject should not bathe, shower or swim for at least 1 hour after application of the product.

Study kits of blinded drug supplies will be dispensed at Baseline and Weeks 1, 3, 6 and 9 to ensure continuous dosing in case the subject is late for subsequent visits.

Dose adjustments are not permitted in this part of the study. Subjects who require a dose adjustment or discontinuation of study drug must be withdrawn from the study (Section 11.4).

7.1.3.2. Part 2 – Open-label

At the Week 12 Visit, subjects who elect to continue into the open-label part of this study will receive supplies of active FMX-101, 4% minocycline foam.

Treatment during this part of the study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment of some or all areas if there is clinical improvement or resolution of the acne in those areas. Even if the treatment is partially or completely temporarily suspended, the subject will be continued in the study and make all scheduled clinic visits. If at any time the acne recurs or worsens, retreatment of the affected areas may be resumed. At each visit, the changes in treatment will be documented.

Sufficient product will be dispensed at each visit to allow continuation of treatment as required. Subjects may be discontinued from the study at any time if their disease becomes refractory or they become intolerant of the product.

7.1.4. Manufacturer

The manufacturer of the investigational product is [redacted].

7.1.5. Labeling of Study Drug

The Sponsor, or designee will label study drug supplies according to the requirements of the Code of Federal Regulations (21CFR§ 210, Subpart G-Packaging & Labeling Control).

The labels of the investigational (test) product will contain appropriate information as required by regional regulatory authorities and include, as needed, the following information:

- Name and address of the Sponsor
- Protocol number
- Product name / dosage form / mode of administration
- Kit Number / Canister Number
- Site number / Subject number
- Name and address of manufacturer
- Date of manufacture
- Lot/batch number
- Canister contents
- Storage conditions
- Caution Statements:
    - "New Drug – Limited by Federal Law to Investigational Use"
    - "Flammable"
    - "Shake well before use"
    - "Keep out of the reach of children"

The composition, pharmaceutical quality, batch number, and expiration date of the investigational (test) product will be traceable via the kit number.

7.1.6. Storage of Study Drug

FMX-101, 4% and vehicle canisters must be stored at 2°C – 8°C until being dispensed to the subjects. Subsequently, they must be stored at 20°C – 25°C (refer to USP Controlled Room Temperature). The investigator will be responsible for the suitable storage of the investigational product in compliance with the storage instructions and must restrict access to the study personnel only.

7.2. Study Drug Accountability

The Investigator will have overall responsibility for the use of the study drug. The Investigator or designee will verify the contents of the drug shipment and confirm receipt of the study drug in the Interactive Web Response System (IWRS) system. In addition, an accurate study drug dispensing record that specifies the date and amount dispensed to each subject must be kept. This inventory record must be available for inspection by representatives of the Sponsor and is subject to regional regulatory authority inspection at any time. At the conclusion of the study, the Investigator must provide a copy of this record to the Sponsor. In addition, the weight of each canister will be determined prior to being dispensed to the subjects and each canister that has been retrieved from the subject will be returned to the vendor to be weighed.

Under no circumstances will the Investigator allow the investigational drugs to be used other than as directed by this protocol. Qualified study personnel must use the IWRS to assign and dispense kits to the subjects. Reasons for digression from the expected dispensing regimen must also be recorded.

7.3. Handling and Disposal of Study Drug

The study drug must be protected from unauthorized access (eg, in a locked storage facility).

Any unused, partially used, or empty bottles of study drug will be returned to the Sponsor or designee by the time of the site's close-out visit. Receipt, distribution, and return of the study drug must be properly documented on forms provided by the Sponsor or designee.

7.4. Method of Assignment of Study Drug

7.4.1. Part 1 – Double- blind

After pretreatment clinical evaluations and all other screening procedures have been completed, authorized site personnel will acknowledge that the applicable subject met all the specified inclusion criteria and none of the exclusion criteria. Assignment to a treatment group will then follow a predetermined list of randomization numbers, with each successive number receiving 1 of the 2 treatments in random order. Authorized site personnel will use the IWRS system to assign a kit number that corresponds to the randomization schedule. The kit box with the assigned kit number will be dispensed to the subject.

The randomization code will be provided by TKL.

7.4.2. Part 2 – Open-label

All subjects who elect to continue into the second part of the study will receive FMX-101, 4% minocycline foam as described in Section 7.1.3.2.

7.5. Selection and Timing of Doses in the Study

The 4% minocycline concentration of FMX-101 was shown to be more effective than 1% in a Phase 2 study. The once-daily dosing regimen is appropriate given the pharmacokinetic characteristics of minocycline.

7.6. Blinding

The first part of this study is double-blind with limited access to the randomization code. The randomization code will be held in confidence until after the study database is locked and a memo documenting the database lock has been issued. Every effort will be made to retain the integrity of the blind. When issued to the sites, the study drug will be identical in appearance for all subjects, regardless of treatment assignment.

The treatment each subject receives will not be disclosed to the Investigator, study site personnel, subjects, monitors, or the Sponsor staff except as required for the purposes of conducting this study.

In the event that emergency identification of study drug is required (eg, if the Investigator believes that the information is necessary to properly treat a subject with an AE), the study drug identity can be obtained by the Investigator through the IRT system.

Before breaking the blind for a subject, the Investigator should determine that the information is necessary (ie, that it will alter the subject's immediate course of treatment and will contribute to the management of the AE). In many cases, particularly when the emergency is clearly not related to study drug, the problem may be effectively managed by assuming that the subject is receiving active study drug without the need for unblinding. Every effort should be made to alert the Medical Monitor before requesting that the blind be broken. If this is not possible, the Medical Monitor should be immediately notified of the breaking of the blind. The Investigator will record the unblinding procedures in the subject's source documents.

If unblinding is necessary, the subject will be withdrawn from the study and Week 12 Visit assessments will be completed.

7.7. Prior and Concomitant Therapy

Subjects should use the cleanser, CCI [redacted] (provided by the Sponsor). An alternative, non-medicated, cleanser may be used if agreed to by the Sponsor.

The use of or change in the dose of any and all concomitant medication, either prescription or over-the-counter, during the study will be recorded. The reason for use or change of dose of a concomitant therapy may need to be reported as an AE. Therapies (medication and non-medication therapies) not restricted by the protocol may be used. Non-prohibited chronic therapies being used at Baseline may be continued. If a subject is using an oral contraceptive product, she should have been on the same product for at least 3 months and she should continue using the same or equivalent product for the duration of the double-blind portion of the study.

If a subject is taking anticoagulant therapy, the subject should be advised that they may require a downward adjustment of their anticoagulant dosage.

All topical or systemic medications listed in the exclusion criteria are prohibited during the double-blind part of this study (through Week 12). Similarly, no other topical medications are permitted to be used on the face during this period. Subjects requiring systemic antibiotics not known to affect acne will be considered on a case-by-case basis. During the open-label part of the study, concomitant acne medications are permitted; their use should be properly recorded.

See the Investigators' Brochure for information about tetracyclines and possible drug-drug interactions

7.8. Use of Contraception

Tetracycline-class antibiotics can cause fetal harm when administered to a pregnant woman. Tetracycline-class antibiotics used during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of teeth (yellow-gray-brown).

Prior to study enrollment, females of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. Females of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea > 12 consecutive months). Females of childbearing potential must have a negative urine pregnancy test and, if they are sexually active or become sexually active during the study, must use an effective method of birth control such as those listed below during the course of the study. The following is not an all-inclusive list; the subject must discuss with the Investigator the most appropriate form of birth control:

- Hormonal methods
    - Oral contraceptives – (Topical antibiotics may lessen the effectiveness of oral contraceptives. Therefore, a second form of birth control must be utilized in subjects using oral contraceptives)
    - Implant
    - Injection
    - Transdermal patch
    - Intravaginal Ring
- Intrauterine Device (hormonal or non-hormonal)
- Barrier methods
    - Condom (male or female) with spermicide
    - Diaphragm with spermicide
- Abstinence

7.9. Treatment Compliance

Each subject is to be instructed on the importance of following the dosing schedule and returning all kits (empty/used/unused) at the appropriate visits. The study personnel will question the subject on the history of study drug use since the last visit. A subject who deviates significantly from the prescribed dosage will be counseled.

8. EFFICACY ASSESSMENTS

8.1. Primary Efficacy Assessments

The primary efficacy assessments will be the IGA and lesion counts.

8.1.1. Investigator Global Assessment Score (IGA)

Table 3 displays the IGA scale for acne vulgaris, which will be used by the investigators to assess the severity of a subject's acne vulgaris. The Case Report Forms (CRFs) will allow for Investigators to report lesions worsening beyond Grade 4 with treatment. The IGA must be performed prior to the lesion count.

The same evaluator should perform all evaluations for a subject; when this is not possible, another approved evaluator may perform the evaluations.

Table 3: IGA Scale for Acne Vulgaris

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions may be present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink- red)
2	Mild	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Many noninflammatory 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
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

8.1.2. Lesion Counts

Subjects are eligible for enrollment if they have:

- 20 to 50 inflammatory lesions (papules, pustules, and nodules)
- 25 to 100 noninflammatory lesions (open and closed comedones)
- No more than 2 nodules can be present on the face at Screening

Lesions will be characterized as inflammatory or non-inflammatory using the following criteria:

- **Inflammatory** lesions:

  Papule – a solid, elevated lesion less than 0.5 cm in diameter

  Pustule – an elevated lesion containing pus less than 0.5 cm in diameter

  Nodule – palpable solid lesion greater than 0.5 cm in diameter; has depth, not necessarily elevated

- **Noninflammatory** lesions:

  Open comedones (blackhead) – non-infected plugged hair follicle with dilated/open orifice; black in color

  Closed comedones (whitehead) – non-infected plugged hair follicle: small (microscopic) opening at skin surface

Facial lesion counts will be made for the forehead, left and right cheeks, nose and chin at each visit. Total inflammatory lesions (pustules, papules, and nodular lesions) and noninflammatory lesions (open and closed comedones) will be counted and recorded separately. Lesion counts will be repeated at Weeks 3, 6, 9 and 12.

8.2. Photography

Photography of the face will be performed at Baseline and at Weeks 6 and 12 using recognized methods. The equipment and techniques for this photography and for archiving the images are described in the Study Manual. Photographs will be reviewed at the site and by the sponsor for quality. Photographs will not be used to assess the lesion counts or the Investigator's assessment of global severity but will be archived to be available for subsequent review, if required, by the sponsor, auditors or the FDA.

8.3. Subject Satisfaction Questionnaire

A satisfaction questionnaire will be administered at Visit 6, Week 12 and Visit 13, Week 52 (see Section 16.1, Appendix 1).

9. SAFETY ASSESSMENTS

The safety assessments in this study are standard safety measures in clinical studies, including physical examinations, the monitoring of vital signs, AEs (volunteered, observed, and elicited by general questioning in a non-suggestive manner), and clinical laboratory test results. In addition, skin assessments at the drug application site(s) will be performed.

9.1. Medical/Surgical History

A complete medical and surgical history will be obtained at Screening, which will include diseases of the head, ears, eyes, nose and throat; respiratory diseases; cardiovascular diseases; gastrointestinal diseases, hepatic diseases, genitourinary diseases, musculoskeletal diseases, endocrine diseases, neurological diseases, psychiatric diseases, skin diseases, allergies, hematological diseases, and other abnormalities.

9.2. Medication History

A history of medication usage (including previous use of acne medications and non-medication therapies) will be recorded at Screening. The start and stop dates of previous use of medications in the last 3 months will be recorded.

9.3. Concomitant Medications

All medication that the subject is currently taking or any change in medication or dosage since the last visit will be documented throughout the study.

9.4. Vital Signs

Heart rate and blood pressure will be measured at all post-Baseline visits. All blood pressure measurements will be made using a sphygmomanometer with an appropriate cuff size for the individual subject. Measurements will be administered while the subject is seated after at least 5 minutes at rest.

9.5. Physical Examination

A complete physical examination will include an evaluation of general appearance, skin, HEENT, neck, lymph nodes, lungs, heart, abdomen, musculoskeletal system, and neurologic system. A standard 12-lead EKG (after at least 5 minutes rest) will be performed at Baseline in subjects over 39 years of age.

Weight will be recorded at the Baseline Visit, Visit 6 (Week 12) and Final Visit (Week 52). Height will be measured at Baseline, only.

9.6. Clinical Laboratory Tests

Serum chemistry, hematology and urinalysis will be evaluated at Baseline, Week 12/ Final Visit of the double-blind phase of the Study, and at Week 28 and Week 52/Final Visit of the open-label phase of the Study. Serum chemistry, hematology, and urinalysis tests will be performed at a central laboratory.

Refer to the manual from the central laboratory for detailed instructions on collecting, processing, and shipping of samples.

Hematology	Urinalysis	Serum chemistry
Hematocrit Hemoglobin MCH MCHC MCV MPV Platelet count RBC RDW WBC Reticulocyte count WBC differential (% & absolute) : Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Glucose Ketones Leukocytes esterase pH Protein Specific gravity Urine pregnancy performed at the site	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartic acid transaminase (AST) Blood urea nitrogen (BUN) Calcium Chloride Cholesterol Creatinine Creatinine kinase Gamma glutamyl transferase (GGT) Globulin Glucose Phosphorus Potassium Sodium Total bilirubin (if elevated obtain direct bilirubin) Total protein Triglycerides Uric acid

9.6.1. Urine Pregnancy Test

A urine pregnancy test will be performed on all females of childbearing potential at Baseline, Week 3, Week 6, Week 9 and Week 12 of the double-blind phase of the Study and Final Visit or when a subject prematurely withdraws from the study.

Home pregnancy kits will be provided at each visit to all female subjects of childbearing potential in the open-label phase of the Study and are to be used at least monthly and if a pregnancy is suspected between visits (e.g., if a subject misses a period). A urine pregnancy test will be performed at Week 52/ Final Visit.

9.6.2. Sample Collection, Storage, and Shipping

Sample collection kits, requisition slips, and shipping boxes will be supplied by the central laboratory. Sample collection procedures and shipping instructions will be detailed in the laboratory manual. Study centers must be equipped to store the samples according to the laboratory manual procedures before shipping samples to the central laboratory.

9.7. Other Safety Measurements

9.7.1. Tolerability

Erythema, dryness, hyperpigmentation and skin peeling at the sites of study drug application will be assessed by the investigator at each study visit on a scale of 0 to 3 (0=none; 1=mild; 2=moderate; 3=severe). Itching will be assessed using the same scale based on the subjects' subjective assessment. The intensity and location of each finding will be recorded. These signs

and symptoms should not be recorded as AEs unless they require concomitant treatment or lead to the subject's discontinuation from the study.

9.8. Adverse Events

9.8.1. Method of Determining Adverse Events

Safety assessments will include recording AEs reported spontaneously by the subject or observed by the Investigator. AEs will be recorded at each visit throughout the study on the appropriate CRF. Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

Subjects should be asked whether, since the time of the last observation or visit, they had any of the following:

- Experienced any changes in well-being
- Used any new medications
- Changed medication regimens (both prescription and over-the-counter)
- Were admitted to a hospital or had any accidents
- Developed unusual headaches or changes in vision

All questions should be of a general nature and should not suggest symptoms.

When an AE is suspected, all relevant evaluations will be carried out and appropriate treatment provided. Additional follow-up will be done as necessary (Section 9.8.4) and recorded in the subject's source documents, and the results will be provided to the Sponsor.

For AE definitions and reporting requirements, refer to Section 9.8.2 and Section 9.8.3, respectively.

9.8.2. Adverse Event Definitions

9.8.2.1. Adverse Events

An adverse event (AE) is any unfavorable or unintended sign, symptom, or disease that appears or worsens in a subject after the subject signs the ICF (and/or Assent Form) for a clinical study.

Examples of what may be considered an AE include any of the following:

- A new illness
- An exacerbation of a sign or symptom of an underlying condition or of a concomitant illness unrelated to participation in the clinical study or an effect of the study drug or comparator drug

No causal relationship with the study drug is implied by the use of the term "adverse event." An exacerbation of a pre-existing condition/illness is defined as a more frequent occurrence or as an

increase in the severity of the pre-existing condition/illness during the study. Planned or elective surgical procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. (If the event meets the criteria for a serious adverse event [SAE], such as an extended hospitalization, it will be considered an SAE). Conditions leading to unplanned surgical procedures may also be AEs.

9.8.2.2. Serious Adverse Events

A "serious adverse event" (SAE) is any AE that:

- Results in death
- Is life-threatening
  (Note: The term "life-threatening" refers to any AE that, as it occurs, puts the subject at immediate risk of death. It does not refer to an AE that hypothetically might have caused death if it were more severe.)
- Results in hospitalization or prolongation of current hospitalization (not including hospitalization for a pre-existing condition that has not increased in severity or frequency from the subject's underlying medical condition prior to entry into the study)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of a subject
- Is another serious (important medical events) events

(Note: Important medical events may not be immediately life-threatening or result in death or hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed 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 development of drug dependency or drug abuse.)

SAEs will be reported by the Sponsor to the regulatory authorities as required.

9.8.2.3. Severity of Adverse Events

"Severity" of the AE refers to the extent to which an AE affects the subject's daily activities and differs from "Serious," which is a regulatory classification. Severity will be categorized according to the following criteria:

- **Mild**: The symptom has a negligible effect or no impairing effect on the subject's normal function.
- **Moderate**: The symptom impairs the subject's normal function to some extent.
- **Severe**: The symptom has an obvious, significantly impairing effect on the subject's normal function.

9.8.2.4. Relationship of Adverse Events to Study Treatments

"Causality" refers to the relationship of the AE to study drug and will be categorized according to the following criteria:

- **Unlikely**: There is no medical evidence to suggest that the AE may be related to study drug usage, or there is another more probable medical explanation.
- **Possible**: There is medical evidence to suggest that there is a reasonable possibility that the AE may be related to study drug usage. However, other medical explanations cannot be excluded as a possible cause.
- **Probable**: There is strong medical evidence to suggest that the AE is related to study drug usage.

9.8.2.5. Adverse Events Expectedness

Expected AEs are defined as those described in the Investigator's Brochure. If an event increases in intensity or severity from that described in the IB, it will be considered unexpected.

9.8.3. Reporting Adverse Events

AEs that occur from the time of informed consent/assent through completion of the last study visit should be reported. Any AE that the Investigator becomes aware of that occurs within 30 days of study completion or withdrawal should also be reported.

Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

Any serious AEs occurring in a subject receiving study drug must be reported to the Sponsor or designee within 24 hours of the site being informed of the event, even if the event does not appear to be drug-related. The report must be made by sending a completed Serious Adverse Event (SAE) Report form to the Sponsor or designee. Any pertinent follow-up information should be provided in a similar manner. Contact information is provided below:

TKL Clinical Pharmacovigilance

CCI [redacted]

9.8.4. Adverse Event Follow-up

Adverse events, and tolerability signs and symptoms greater than zero (0), that are ongoing when a subject withdraws from or completes the study will be followed until resolution or stabilization (in the opinion of the Investigator), or for 30 days, whichever is shorter. Investigators and the Sponsor will decide if longer follow-up is appropriate on a case-by-case basis. Subjects who experience any clinically significant AE will remain under medical supervision until the Investigator or the Sponsor's Medical Monitor deems the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up.

Laboratory values that are abnormal and not assessed as AEs may be followed at the discretion of the Investigator or the Sponsor's Medical Monitor until resolved or stabilized.

9.8.4.1. Pregnancy reporting

Prior to study enrollment, females of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The Informed Consent or Assent Form that the subject signs must document this discussion.

If a subject or Investigator suspects that the subject may be pregnant prior to study drug administration, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study drug and must not be enrolled in the study.

A urine pregnancy test will be performed on all females of childbearing potential at Baseline, Week 3, Week 6, Week 9 and Week 12 of the double-blind phase of the Study and Final Visit or when a subject prematurely withdraws from the study.

Home pregnancy kits will be provided at each visit to all female subjects of childbearing potential in the open-label phase of the Study and are to be used at least monthly and if a pregnancy is suspected between visits (e.g., if a subject misses a period). A urine pregnancy test will be performed at Week 52/Final Visit.

During the study, all females of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period). If a subject or Investigator suspects that the subject may be pregnant at any time before or during the study, the study drug must be withheld until the results of laboratory pregnancy testing are available. The Sponsor and Site Monitor must be notified and available information captured on a "Suspected Pregnancy" form. If pregnancy is confirmed, the subject must be withdrawn from the study and the Sponsor and Site Monitor notified. Additional relevant information about the confirmed pregnancy will be recorded on the appropriate form(s) but the pregnancy will not be captured as an AE.

The subject should be followed until the outcome of the pregnancy is known.

9.8.5. Clinically Significantly Abnormal Laboratory Results

All laboratory values that are outside of the normal range for that parameter will be so flagged when reported to the site. The Investigator will determine which out-of-range laboratory test results should be characterized as clinically significant and will so annotate the laboratory report. If a clinically significant laboratory abnormality requires treatment or is the reason for a subject being discontinued from the study, the abnormal result must also be classified as an AE.

9.9. Appropriateness of Safety Measurement

The safety assessments in this study are standard safety measures in clinical trials.

10. STATISTICAL DESIGN AND ANALYSIS

10.1. Statistical Analysis Plan

A detailed statistical analysis plan will be finalized prior to breaking of the study blind.

Descriptive statistics for qualitative variables (eg, race) will include the number and percentage of subjects with the qualitative response. Missing responses will be enumerated, but the calculation of percentages will exclude missing responses. For quantitative variables (eg, age), descriptive statistics will include the number of subjects with non-missing data, mean, standard deviation, median, minimum value and maximum value. All hypothesis testing will be conducted using two-sided tests with α=0.05 level of significance unless otherwise specified.

All study data will be presented in listings.

10.2. Determination of Sample Size

In a phase 2 study, the proportion of subjects with an IGA score of 0 or 1 after 12 weeks of treatment was 20% in the minocycline 4% foam group compared to 2% in the vehicle group. The following table provides a few alternate assumptions and corresponding sample sizes. Power was set to 90% and type-1 error to two-sided 0.05. Sample size was calculated based on Fisher's Exact test.

Vehicle IGA (0,1)	Minocycline 4% foam IGA (0,1)	Sample sizes (vehicle, active)
CCI	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI

Assuming 12% dropout rate, CCI subjects on active, and CCI subjects on vehicle will provide at least 90% power for a statistically significant difference on IGA 0 or 1. In the same phase 2 study, the change from baseline in inflammatory lesions was CCI in the minocycline 4% foam versus CCI in the vehicle group. The standard deviation in change from baseline was approximately 9.2. The following table shows alternate assumptions and corresponding sample sizes, for 90% power and a two-sided type 1 error of 0.05. The sample sizes were calculated using a t-test.

Vehicle mean inflammatory lesion reduction	Minocycline 4% foam mean inflammatory lesion reduction	Sample sizes (vehicle, active)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

To summarize, using some conservative estimates of the effect on minocycline 4% foam versus the vehicle for both IGA and change in inflammatory lesions at week [redacted] subjects on active, and [redacted] on vehicle will provide > 90% power for s statistically significant difference.

Another consideration for the sample size must be given to the secondary endpoint of noninflammatory lesions which will be compared to the vehicle for non-inferiority. The margin for non-inferiority will be 30% of the change from baseline to week 12. In a phase 2 study, change from baseline in noninflammatory lesions at week 9 was [redacted] for the vehicle group with a standard deviation of 18. Assuming approximately the same reduction at week 12, a 30% non-inferiority margin is about [redacted] lesions. The following table provides approximate sample sizes for alternate assumptions for 90% power to show non-inferiority.

Vehicle mean noninflammatory lesion reduction	Minocycline 4% foam mean noninflammatory lesion reduction	Sample sizes (vehicle, active)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

If Minocycline 4% foam has the same effect on noninflammatory lesions as vehicle, [redacted] subjects on vehicle and [redacted] on 4% foam will be needed for 90% power to show non-inferiority. If Minocycline 4% foam has a slightly less effect on noninflammatory lesions ([redacted] lesion reduction versus [redacted] in vehicle), there will be about 90% power to show non-inferiority.

10.3. Analysis Populations

The Intent-to-Treat (ITT) population will include all randomized subjects. The ITT population will be the primary population for all efficacy analyses.

The Safety population will include all randomized subjects who took at least one dose of study drug. Subjects who have no post-Baseline assessments will be included in the Safety population unless all dispensed study drug is returned unused.

The Per Protocol (PP) population is defined as the subset of the ITT population without any protocol deviations that may have an impact on the efficacy assessments. The subjects to be

included in the PP population will be determined by the Sponsor/CRO prior to the unblinding of the study. The PP population will be secondary for the co-primary endpoints only.

Subjects may be excluded from the PP population if any of the following are met:

- Did not meet inclusion/exclusion criteria
- Have administered any interfering concomitant medications
- Have not, in the opinion of the investigator, been compliant with the treatment regimen (e.g. reported frequent missed doses)

Prior to breaking the blind, additional criteria for exclusion from the PP population may be included to accommodate for unforeseen events that occurred during the conduct of the study.

10.4. Efficacy Endpoints

The primary population for all efficacy analyses will be the ITT population. Subjects will be analyzed according to their randomized treatment. The primary method of handling missing data will be the last observation carried forward (LOCF) approach. Sensitivity analyses using multiple imputations and baseline observation carried forward (BOCF) will be performed on the co-primary endpoints only.

Supportive efficacy analyses will also be performed on the PP population. All analyses using the PP population will use the Observed-Cases (OC) approach. i.e., there will be no imputation for missing data at any time point.

Changes from Baseline lesion count will be calculated as the Baseline value minus the post-Baseline value. Thus, a positive change will reflect a reduction in lesion count. The percent change from Baseline lesion count will be calculated as the Baseline value minus the post-Baseline value divided by the Baseline value, expressed as a percentage. Thus, a positive percent change will reflect a reduction in lesion count.

10.4.1. Primary Efficacy Endpoints

The co-primary efficacy endpoints are:

- The absolute change from Baseline in the inflammatory lesion count at Week 12
- Treatment Success (dichotomized as Yes/No) at Week 12, where success is defined as an IGA score of 0 or 1, and at least a 2-grade improvement (decrease) from Baseline

The null hypotheses of the equality of the FMX-101 4% and vehicle means for absolute change from Baseline to Week 12 in the inflammatory lesion count and the equality of IGA success rates at Week 12 will each be tested at a two-sided 0.05 level of significance. Change from baseline in inflammatory lesion count will be analyzed using an Analysis of Covariance (ANCOVA), with Treatment as a main effect, baseline inflammatory lesion count as a covariate, and investigational site a blocking factor. Investigational site by Treatment interaction will be tested at 0.1 level, and if significant, it will further be explored. The dichotomized IGA will be analyzed using a Cochran-Mantel-Haenszel (CMH) test, stratified by investigational site.

10.4.2. Secondary Efficacy Endpoints

- The absolute change from Baseline in the noninflammatory lesion count at Week 12
- The absolute change from Baseline in the inflammatory lesion count and IGA Treatment Success at the interim visit at Week 9
- The absolute change from Baseline in the inflammatory lesion count and IGA Treatment Success at the interim visit at Week 6

10.4.3. Tertiary efficacy endpoints

- The percent change from Baseline in the inflammatory lesion count at Weeks 3, 6, 9 and 12
- The absolute change from Baseline in the inflammatory and noninflammatory lesions, and the IGA Treatment Success at Week 3
- The absolute change from Baseline in the noninflammatory lesion count at Weeks 3, 6, 9 and 12
- The percent change from Baseline in the noninflammatory lesion count at Weeks 3, 6, 9 and 12

Secondary efficacy endpoint will be tested sequentially in the order listed above, at 0.05 level of significance, only if the co-primary efficacy endpoints are significant.

10.5. Safety endpoints

Treatment-emergent adverse events (TEAEs), vital signs, physical examinations, and clinical laboratory measurements will be reported on the Safety population. Subjects will be reported according to the treatment they actually received. No statistical tests will be performed for any of the safety assessments.

Baseline for vital signs, physical examinations, and clinical laboratory measurements is defined as the last non-missing value prior to the first dose of study drug.

10.5.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) terminology will be used to classify all AEs with respect to system organ class (SOC) and preferred term.

TEAEs will be defined as events that emerge during treatment having been absent pre-treatment, or worsen relative to the pre-treatment state. Summaries of AEs will be limited to TEAEs. The number and percentage of subjects reporting each SOC and preferred term will be summarized for each treatment group and by the Study Period. At each level of summarization, a subject will be counted once if he/she reported one or more events. The severity of TEAEs and relationship to study drug will be summarized in a similar manner. For summaries of relationship to study drug, a subject will be classified according to the closest relationship. For summaries of TEAE severity, a subject will be classified according to the highest severity.

Summaries of SAEs and subjects who prematurely withdraw from the study due to AEs will be presented.

10.5.2. Vital Signs

Vital sign parameters will be summarized using descriptive statistics at Baseline and at each post-baseline time point. Changes from Baseline will also be summarized. Baseline is defined as the last non-missing value prior to the first dose of study drug.

10.5.3. Physical Examinations

Physical examinations will be summarized using descriptive statistics at Baseline and at each post-baseline time point. Shifts from Baseline will also be summarized. Baseline is defined as the last non-missing value prior to the first dose of study drug.

10.5.4. Clinical Laboratory Results

Baseline is defined as the last non-missing value prior to the first dose of study drug.

Shift tables for each clinical laboratory test will cross-tabulate the number of subjects with values below the laboratory reference range (low), values within the laboratory reference range (normal) or above the laboratory range (high) at baseline with the number of subjects with low, normal or high values at each post-baseline time point.

A listing of subjects with pre-treatment and treatment-emergent clinically significant abnormal laboratory values will be presented for each treatment group. Clinical significance is based on the Investigator's judgment.

10.6. Statistical Analysis

10.6.1. Interim Analysis

No interim analysis is planned.

10.6.2. Subject Accounting, Demographic, and Baseline Characteristics

Demographic, baseline characteristics, and prior and concomitant medications will be summarized by treatment. Study completion status and reasons for discontinuation will also be displayed by treatment.

Medical and surgical history will only be presented in the listings.

10.6.3. Efficacy Analysis

The co-primary endpoint of absolute change from Baseline in inflammatory lesions at Week 12 will be analyzed using an Analysis of Covariance (ANCOVA) model with main effect treatment and investigational site as a covariate. The treatment by investigational site interaction will be tested separately at 0.1 level of significance, and if significant, will be further be explored. A 95% confidence interval will be calculated on the difference in mean changes from baseline between FMX-101 4% and vehicle.

The co-primary endpoint of IGA Treatment Success rate at Week 12 will be analyzed using a Cochran–Mantel–Haenszel (CMH) test with investigational site as the stratification factor. If the overall IGA Treatment Success rate is less than 10%, a Fisher's Exact test will be used to

corroborate the CMH test. A 95% confidence interval will be constructed on the difference in IGA Treatment Success rates between FMX-101 4% and vehicle.

If FMX-101, 4% is found superior to vehicle (one-sided p<=0.025) for both co-primary endpoints, the secondary endpoints will be tested sequentially. The first secondary endpoint of noninflammatory lesions at Week 12 will be tested initially as a non-inferiority comparison of FMX-101, 4% to vehicle. Non-inferiority margin is defined as 30% of the noninflammatory lesion reduction in the vehicle group at Week 12. A lower 97.5% confidence limit will be calculated for μ_a-0.6×$\mu_{v,}$ where μ_a and μ_v are the mean reduction of noninflamatory lesions of FMX-101, 4% and vehicle respectively. If the confidence limit is above 0, non-inferiority will be concluded. If non-inferiority is concluded, the superiority of FMX-101, 4% to vehicle for noninflammatory lesions at Week 12 will be tested. The sequential testing will proceed according to the order in Section 10.4.2.1. Testing of secondary efficacy endpoints at an earlier timepoint for each type of lesion and IGA Treatment Success will be performed only if superiority (one-sided p<=0.025) is seen at the later timepoint.

Secondary efficacy parameters will be analyzed similar to the appropriate co-primary efficacy parameter.

Absolute change from baseline in inflammatory lesion count and the IGA assessments in the open-label phase of the study will be summarized. No statistical testing will be performed for the open label efficacy data.

10.6.4. Safety Analysis

The Medical Dictionary for Regulatory Activities (MedDRA) terminology will be used to classify all AEs with respect to system organ class (SOC) and preferred term.

TEAEs will be defined as events that emerge during treatment having been absent pre-treatment, or worsen relative to the pre-treatment state. Summaries of AEs will be limited to TEAEs. The number and percentage of subjects reporting each SOC and preferred term will be summarized for each treatment group. At each level of summarization, a subject will be counted once if he/she reported one or more events. The severity of TEAEs and relationship to study drug will be summarized in a similar manner. For summaries of relationship to study drug, a subject will be classified according to the closest relationship. For summaries of TEAE severity, a subject will be classified according to the highest severity.

Summaries of SAEs and subjects who prematurely withdraw from the study due to AEs will be presented.

Vital sign parameters will be summarized using descriptive statistics at Baseline and at each post-baseline time point. Changes from Baseline will also be summarized.

Physical examinations will be summarized using descriptive statistics at Baseline and for the final visit. Shifts from Baseline will also be summarized.

Shift tables for each clinical laboratory test will cross-tabulate the number of subjects with values below the laboratory reference range (low), values within the laboratory reference range (normal) or above the laboratory range (high) at baseline with the number of subjects with low, normal or high values at the Final Visit.

A listing of subjects with pre-treatment and treatment-emergent clinically significant abnormal laboratory values will be presented for each treatment group. Clinical significance is based on the Investigator's judgment.

11. STUDY MANAGEMENT

11.1. Monitoring

The Investigator will be responsible for preparing and maintaining adequate and accurate source documents (medical records, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject treated with the study drug. The Investigator will allow representatives of the Sponsor, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study. The Investigator is to immediately notify the Sponsor or the Sponsor's representative of any regulatory authority inspections. The Investigator will be informed about the outcome of any Sponsor audit.

This study will be monitored regularly, by or under supervision of a monitor from the Sponsor. The frequency of monitoring visits will be agreed upon by the Sponsor's representative and the study site.

Monitoring visits will take place on a regular basis according to the enrollment rate and number of subjects enrolled at each investigational site. During these visits, the monitor will check the completion of the CRF entries, compliance with the study protocol and with GCP-ICH, and the agreement of key entries with the source data. The monitor will also verify the correct use of the study drug. At the Final Visit or at an agreed to time prior to the Final Visit, the monitor will check all remaining material including the remaining quantities of the study drug and will organize their return to the Sponsor or designee. At each visit, the Investigator and staff will be expected to cooperate with the Sponsor's representative(s) for the purposes of review and verification of protocol compliance, AE reporting, CRFs, source documents, clinical supplies and inventory records, and any additional records as may have been previously arranged between the Investigator and the Sponsor's representative(s).

The Investigator and/or other designated study personnel are expected to contact the Sponsor's or the Sponsor's representative's clinical research associate, as needed, regarding study concerns and/or questions. Contact information is provided in the Study Binder for the site.

11.2. Protocol Amendments

The Sponsor may propose to amend this protocol at any time.

No change to the protocol will be implemented until the Sponsor and the IRB have reviewed and approved the amendment.

In the event of an emergency, the Investigator shall implement any medical procedures deemed appropriate for subject safety. All such procedures must have written documentation and be promptly reported to the Sponsor.

Amendments to the protocol, if any, are included in Section 16.2, page 53. This protocol version includes Amendment 1, effective February 26, 2016 and Amendment 2, effective April 6, 2016.

11.3. Protocol Deviations

A protocol deviation is any change, divergence or departure from the IRB-approved protocol by the study staff (intentional or unintentional). All deviations are to be documented at the site and reported to the IRB according to the IRB's guidelines.

In the event of an emergency, the Investigator shall implement any medical procedures deemed appropriate for subject safety. All such procedures must have written documentation and be promptly reported to the Sponsor.

11.4. Withdrawal of Subjects

Withdrawn subjects are those who do not complete all evaluations and procedures outlined in the protocol. Subjects who discontinue taking study drug for any reason must also be withdrawn from the study. Subjects may be withdrawn from the study because of one of the following:

- **Adverse Event:** An AE that, in the opinion of the Investigator or Sponsor, suggests that continued participation in the study is not in the subject's best interest for safety reasons. All AEs that are present when the subject withdraws from the study will be followed as described in Section 9.8.4.
- **Abnormal Laboratory Result:** Any clinically significant laboratory abnormality that requires withdrawal of the subject from the study should be considered an AE leading to withdrawal. If possible, laboratory tests will be repeated for any results that were clinically significantly abnormal until the abnormality is resolved or stabilized to the satisfaction of the Investigator in consultation with the Medical Monitor.
- **Lost to Follow-up:** Confirmed at minimum by 2 phone calls and a traceable letter without response.
- **Subject Request:** Subject requests, for any reason (eg, AE), to be withdrawn or withdraws his/her consent.
- **Poor protocol adherence:** A subject may be withdrawn from the study at the discretion of the Investigator or Sponsor due to poor compliance with protocol requirements that may compromise the study results or subject safety.
- **Other:** Other reasons include but are not limited to: Investigator decision that it is in the subject's best interest to be withdrawn, administrative reasons, relocation of subject, etc. If a subject becomes pregnant during the study, the subject will be withdrawn from the study and followed through conclusion of the pregnancy.

If a subject is withdrawn from the study following the start of study drug during Period 1 of the study, all Week 12 assessments should be completed. If a subject is withdrawn from the study following the start of study drug during Period 2 of the study, all Final Visit assessments should be completed. Subjects withdrawn from the study will not be replaced.

11.5. Termination of the Study

The study may be terminated at any time at the request of the Sponsor or a regulatory authority, with proper and timely notification of all parties concerned. The IRB will be informed promptly and the Sponsor or the Investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements. Otherwise, the study is considered terminated upon completion of all subject treatments and evaluations.

11.6. Publication Policy

The data obtained in this study are the property of the Sponsor, which will make reasonable efforts to assure that the results are published in a peer-reviewed journal. As some of the information concerning the investigational product and development activities at the Sponsor may be of strictly confidential nature, any manuscript or other presentation of data must first be reviewed by the Sponsor before its submission.

12. ETHICS

12.1. Conduct of the Study

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP, 1997; the US Title 21 CFR parts 50, 56, and 312; and the ethical principles that have their origin in the Declaration of Helsinki. The study will not begin until all of the requirements of the appropriate regulatory authorities have been fulfilled.

12.2. Institutional Review Boards (IRB)

This protocol (and any changes), all consent/assent forms, and subject consent procedures must be reviewed and approved by a properly constituted IRB. The information presented to the IRB at the time initial approval is sought must include any plans for subject recruitment that involve advertising or other direct contact with potential subjects outside of the doctor-subject relationship. A letter of approval issued by the IRB must be sent to the Sponsor prior to initiation of the study. Any changes made to the protocol must be approved by the IRB prior to implementation, except where needed to eliminate a potential imminent safety hazard to the subjects. In this case, immediate implementation may apply place followed by IRB approval. Review and approval by the IRB for continuation of the study must apply place at least once a year.

12.3. Written Informed Consent

The Investigator or designee will explain the nature of the study, its purpose and associated procedures, the expected duration and the potential benefits and risks of participation to each subject prior to his/her entry into the study (ie, before examinations and procedures associated with selection for the study are initiated). Each subject will have ample opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Following this informative discussion, the subject will be asked if he/she is willing to sign a statement of informed consent. Only subjects who voluntarily sign the Informed Consent Forms (ICF) may enter the study. Subjects less than 18 years of age (or as required by state law) must sign an Assent Form for the study and a parent or legal guardian must sign the ICF.

The ICF and Assent Form must be reviewed and approved by the Sponsor and the IRB prior to their use.

The original signed ICF and Assent Form will remain in the Investigator's files. The Investigator or designee will indicate in each subject's source documents that he / she has informed the subject about the study and its procedures, the subject has signed and dated the ICF/Assent Form, and the subject has been given a copy of the documents. The Investigator or designee will inform subjects of any new information that may be relevant to the subjects' willingness to continue in the study.

12.4. Subject Confidentiality

The Sponsor ensures that the following have permission to review all study-related documents: monitor, auditor, IRB and regulatory authorities. The subject's identity and study-related records will remain confidential throughout the duration of the study data collection and reporting process.

A unique subject identification code is assigned to each potential study subject. The identification code protects the subject's identity and is used in lieu of the subject's name when reporting subject data. The data will always maintain the confidentiality of the subject.

The investigator or designee will review the subject data, which will be referenced using the subject identifier. At the conclusion of the study, the data obtained may be presented to regional regulatory authorities but the subject's identity will not be revealed. In addition, if any clinical data obtained from the study is published in scientific journals or presented at scientific meetings the subject's identity will not be revealed.

12.5. Records Retention

The Investigator must maintain essential study documents (protocol and amendments, source documentation corresponding to all information contained in the CRFs, signed informed consent and assent forms, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same time period. Custody of the records may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notice of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

12.6. Financing

Funding for this study will be agreed between the Investigator and the Sponsor and will be confirmed in writing before the study starts.

Completion of Financial Disclosure Forms will be required before the study starts. Any additions to the primary site personnel will necessitate the completion of new Financial Disclosure Forms. This information will also be collected at site closure and one year after the completion of the study.

Disclosure Forms. Investigators will be informed that they must report any new information to the sponsor or designate at site closure and one year after the completion of the study.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and Investigator will apply all steps possible to ensure the accuracy, consistency, completeness, and reliability of the data, including participating in an Investigator meeting and/or site initiation visit, routine site monitoring, review of CRFs against source documents, and quality control checks.

In addition, a representative from the Sponsor's Clinical Quality Assurance (CQA) Department or designee may conduct periodic audits of the study processes, including, but not limited to, auditing the clinical site, laboratories, vendors and CROs, the clinical database, and the final study report.

14. DATA HANDLING AND RECORD KEEPING

This study will use web-based, electronic case report forms (eCRFs) developed through a validated, Electronic Records / Electronic Signatures-compliant platform (US Title 21 CFR Part 11). Foamix Clinical Data Management department or designee will create the electronic CRFs and corresponding clinical database based on the final protocol.

All site personnel who will be using this system will receive formal training on the system, after which each person will be issued a unique user name and password. Only the person who owns the user name and password will enter the system using that user name and password. For data security reasons and to be in compliance with regulatory guidelines, usernames and passwords are not transferable.

The Investigator is responsible for all data entered via the eCRFs and must confirm the accuracy of the data by electronically approving (signing) the eCRFs. This responsibility includes the timely completion and accuracy of the data entered into the eCRFs by their site personnel as well as the review of some data entered directly into the database (eg, clinical laboratory results) by an external vendor. The Sponsor will review the database to identify data errors or inconsistencies, which will be posted in the RDC system as queries for resolution. In addition, the Sponsor may make obvious corrections to the data in the database (eg, obvious errors in dates) and so inform the Investigator without issuing a query to the site.

15. REFERENCE LIST

1. Brown SK, Shalita A R; Acne Vulgaris, Follicutitis, and Acne Rosacea. Lancet 351:1871-76, 1998
2. Guidance for Industry: "Acne Vulgaris: developing Drugs for Treatment " September 2005 FDA Draft Guidance

16. APPENDICES

16.1. Appendix 1 – Subjects Satisfaction Questionnaire

The following 8 questions will be asked of the subject at Visit 6, Week12 and Visit 13, Week 52:

1. How satisfied are you with this product in treating your acne?
2. How satisfied are you with how easy this product is to use?
3. How satisfied are you with this product compared to other products you have previously used for acne, such as gels and creams?
4. How satisfied are you with how this product feels on your skin after treatment?
5. How satisfied are you with the odor of this product after treatment?
6. How satisfied are you with the color of this product after treatment?
7. Overall, how satisfied are you with this product?
8. Overall, how likely are you to recommend this product to a friend?

Answers to Questions 1-7 will be selected from the following:

1=Very Satisfied

2=Satisfied

3=Somewhat Satisfied

4=Dissatisfied

5=Very Dissatisfied

Answer to Question 8 will be selected from the following:

1=Very Likely

2=Likely

3=Somewhat Likely

4=Unlikely

5=Very Unlikely

16.2. Appendix 2 – Protocol Amendments

This appendix describes the amendment(s) that have been made to the protocol for Study FX2014-0.

Section 16.2.1 describes the changes made to Protocol FX2014-05 Version 1 issued January 19, 2016, via Amendment 1 effective February 26, 2016.

Section 16.2.2 describes the changes made to Protocol FX2014-05 Version 2 issued February 26, 2016, via Amendment 2 effective April 6, 2016.

16.2.1. Amendment 1, effective February 26, 2016

The following is the summary of the changes that were made to Protocol FX2014-05 Version 1 issued 19-JAN-2016.

Administrative changes:

Section	Revision
Title Page	Added: PPD
Signature Page	Added
Study Administrative Structure	Added: PPD
SAE Reporting Information	Added: TKL Clinical Pharmacovigilance CCI

Content changes:

New or changed test is **bolded.**

Section	Revision		Rationale
	Old Text	**New Text**	
1.10.1. Efficacy	. . Weeks **1,** 3, 6, 9 and 12	. Weeks 3, 6, 9 and 12.	Correction
1.11 Statistical Methods	IGA **score at** Week 12 (where success is defined as **at least a 2-grade decrease from Baseline)**.	IGA **Treatment Success (dichotomized as Yes/No) at** Week 12, where success is defined as **an IGA score of 0 or 1, and at least a 2-grade decrease from Baseline.**	Modified as per FDA suggestion
	At least a 2-grade improvement (decrease) from Baseline in the IGA score will be analyzed using . . .	**The IGA Treatment Success rates will be compared between the treatment groups using . . .**	

Section	Revision		Rationale
	Old Text	**New Text**	
6. Study Procedures	Inserted	**Procedures at the Screening Visit will include obtaining blood and urine samples for clinical laboratory tests. These results must be no more than 30 days old at the time of Baseline Visit randomization.**	Clarification of timing of laboratory tests during Screening
6. Study Procedures – Table 1	Inserted	"**X**" for Tolerability Assessment at all post-Baseline visits	Added at request of FDA
	"**X**" for Blood and urine samples at Baseline	"**X**" for Blood and urine samples at Screening	Sampling moved to earlier timepoint
	Inserted	"**X**" for Blood and urine samples at Week 3	Added at request of FDA
	Inserted	"**X**" for Dispense study drug at Week 1	Correction
	Inserted	"**X**" to Confirm next visit	Correction
	Footnote inserted	Footnote 6 - **Home pregnancy tests will be dispensed to all female subjects at risk of becoming pregnant and will be performed whenever there is a suspicion of pregnancy (e.g., a missed period)**	Added at request of FDA
6. Study Procedures – Table 1 Footnote 2	If a subject prematurely withdraws from the study, all evaluations described under Visit 6/Week 12 must be performed.	**Subject may continue into open-label phase of study. If a subject is not continuing into open-label phase for any reason (see Section 4.1.2),** all evaluations described under Visit 6/Week 12 must be performed.	Clarification of process at Visit 6
6.1 – 6.2 Study Procedures at Visits 3 – 14	Record AEs	Record AEs **and Tolerability Assessments**	Changed at all post-Baseline Visits at request of FDA
6.1.1 Screening Visit	**Using the Interactive Web Response system (IWRS),** assign the subject a . . .	Assign the subject a . . .	Screening number will not be assigned by IWRS

Section	Revision		Rationale
	Old Text	**New Text**	
	Inserted	• **Collect blood and urine samples for clinical laboratory tests . . .**	Lab tests moved from Baseline to Screening Visit
6.1.2 Baseline Visit, Visit 1	• **Confirm eligibility**	none	Deleted repetition
	• **Collect blood and urine samples for clinical laboratory tests . . .**	deleted	Lab tests moved from Baseline to Screening Visit
6.1.3 Visit 2, Week 1	Inserted	• **Dispense 1 kit (2 canisters) of study drug**	Correction
6.1.4. Visit 3, Week 3	inserted	• **Collect blood and urine samples for clinical . . .**	Added per FDA request
	• **Confirm that subject continues to use the drug product and only provided cleanser correctly**	Deleted	Redundant
6.1.7. Visit 6, Week 12	End of Double-Blind or Early Termination	End of Double-Blind or **Continuation in Open Label /** Early Termination	Title changed for clarity
6.2 Part 2 – Open-label Table 2	Footnote inserted	Footnote 3 - **Home pregnancy tests will be dispensed to all female subjects at risk of becoming pregnant and will be performed whenever there is a suspicion of pregnancy (e.g., a missed period)**	Added at request of FDA
	Inserted	"**X**" for Tolerability Assessment at all post-Baseline visits	Added at request of FDA
	Inserted	"**X**" for Blood and urine samples at Week 28	Added at request of FDA
6.2.1 Visit 7 – Week 16	Dispense **1** kits (**2** canisters) of FMX-101, 4% minocycline foam if required	Dispense **2** kits (**4** canisters) of FMX-101, 4% minocycline foam if required	Correction
6.2.2 Visit 9, Week 28	inserted	• **At Visit 9 (Week 28) only – Collect blood and urine . . .**	Added per FDA request
7.1.3.1 Part 1 – Double-blind	none	**After shaking the canister well** . . .	Added text to include instruction to shake
	. . .supplies will be dispensed at Baseline and Weeks 3, 6 and 9 . . .	. . . supplies will be dispensed at Baseline and Weeks **1**, 3, 6 and 9 . . .	Correction

Section	Revision		Rationale
	Old Text	**New Text**	
7.1.5 Labeling of Study Drug	none	**"Shake well before using"**	Added text to label about shaking
7.1.6 Storage of Drug	FMX-101, 4% and vehicle canisters must be stored at 20°C – 25°C . . .	FMX-101, 4% and vehicle canisters must be stored at **2°C – 8°C until being dispensed to the subjects. Subsequently, they must be stored at** 20°C – 25°C . . .	Inclusion of instruction that site must keep drug refrigerated until it is dispensed
7.2 Study Drug Accountability	Inserted	**In addition, the weight of each canister will be determined prior to being dispensed to the subjects and each canister that has been retrieved from the subject will be returned to the vendor to be weighed**	Added per FDA request
7.7 Prior and Concomitant Therapy	Inserted	**If a subject is taking anticoagulant therapy, the subject should be advised that they may require a downward adjustment of their anticoagulant dosage.**	Tetracyclines may decrease plasma prothrombin activity
7.8 Use of Contraception	• Hormonal methods o Oral contraceptives . . . birth control must be utilized in subjects using topical contraceptives)	• Hormonal methods o Oral contraceptives . . . birth control must be utilized in subjects using **oral** contraceptives)	Correction
8.1.1 IGA Table 3	See a) below	See b) below	Removal of quantitative description of non-inflammatory lesions

Section	Revision		Rationale
	Old Text	**New Text**	
8.1.2 Lesion counts	Facial lesion counts . . . Inflammatory lesions (pustules, papules, and nodular lesions) and noninflammatory lesions (open and closed comedones) will be counted **for each area** and recorded separately. **The totals of inflammatory and non-inflammatory lesions will be calculated from these regional lesion counts.** Lesion counts will be repeated at Weeks 3, 6, 9 and 12. **Totals do not need to be calculated at these visits**.	Facial lesion counts . . . **Total** inflammatory lesions (pustules, papules, and nodular lesions) and noninflammatory lesions (open and closed comedones) will be counted and recorded separately. Lesion counts will be repeated at Weeks 3, 6, 9 and 12.	Counting method modified and addressed in Data Management Plan
9.2 Medication History	A history of medication usage . . . medications in the last 3 months **(6 months for acne medications)** will be recorded.	A history of medication usage . . . medications in the last 3 months will be recorded.	Consistency with Section 6.1.1.
9.4 Vital Signs	Heart rate and blood pressure will be measured at all visits.	Heart rate and blood pressure will be measured at all **post-Baseline** visits.	Correction
9.8.1 Method of Determining Adverse Events	inserted	• **Developed unusual headaches or changes in vision**	Queried at each visit as per FDA request
9.8.3. Reporting Adverse Events	Any serious AEs . . . must be reported to the Sponsor within . . .	Any serious AEs . . . must be reported to the Sponsor **or designee** within . . .	Correction of omission
10.2 Determination of Sample Size	None	See text at c) below	Modified as per FDA suggestion
10.4.1 Primary Efficacy Endpoints	IGA **score at** Week 12 (where success is defined as **at least a 2-grade decrease from Baseline)**.	**Treatment Success (dichotomized as Yes/No) at** Week 12, where success is defined as **an IGA score of 0 or 1, and at least a 2-grade improvement (decrease) from Baseline.**	Modified as per FDA suggestion

Section	Revision		Rationale
	Old Text	**New Text**	
10.4.2. Secondary Efficacy Endpoints	• The absolute change from Baseline in the noninflammatory lesion count at Week 12 • The absolute change from Baseline in the inflammatory lesion count and IGA at the interim visit at Week 9 • **The absolute change from Baseline in the noninflammatory lesion count at Week 9** • The absolute change from Baseline in the inflammatory lesion count and IGA Treatment Success at the interim visit at Week 6 • **The absolute change from Baseline in the noninflammatory lesion count at Week 6**	• The absolute change from Baseline in the noninflammatory lesion count at Week 12 • The absolute change from Baseline in the inflammatory lesion count and IGA **Treatment Success** at the interim visit at Week 9 • The absolute change from Baseline in the inflammatory lesion count and IGA **Treatment Success** at the interim visit at Week 6	Modified as per FDA suggestion
10.4.3. Tertiary Efficacy Endpoints	• The percent change from Baseline in the inflammatory lesion count at Weeks 3, 6, 9 and 12 • **The percent change from Baseline in the noninflammatory lesion count at Weeks 3, 6, 9 and 12** • The absolute change from Baseline in the inflammatory and noninflammatory lesions, and **the dichotomized IGA score, (where success is defined as at least a 2-grade decrease from Baseline),** at Week 3 • The percent change from Baseline in the noninflammatory lesion count at Weeks 3, 6, 9 and 12	• The percent change from Baseline in the inflammatory lesion count at Weeks 3, 6, 9 and 12 • The absolute change from Baseline in the inflammatory and noninflammatory lesions, and the IGA **Treatment Success** at Week 3 • **The absolute change from Baseline in the noninflammatory lesion count at Weeks 3, 6, and 9** • The percent change from Baseline in the noninflammatory lesion count at Weeks 3, 6, 9 and 12	Modified as per FDA suggestion

Section	Revision		Rationale
	Old Text	**New Text**	
10.6.3 Efficacy Analysis	The co-primary endpoint of **at least a 2-grade improvement (decrease) from Baseline in the IGA score** at Week 12 will be analyzed . . . overall **IGA response rates** are less than 10% . . . on the difference in **IGA success** rates between FMX-101 4% and vehicle.	The co-primary endpoint of **IGA Treatment Success rate** at Week 12 will be analyzed . . . overall **IGA Treatment Success rate** is less than 10% . . . on the difference **in IGA Treatment Success** rates between FMX-101 4% and vehicle.	Modified as per FDA suggestion
	. . .Testing of secondary efficacy endpoints at an earlier timepoint for each type of lesion and IGA will be performed only if superiority (one-sided p<=0.025) is seen at the later timepoint.	. Testing of secondary efficacy endpoints at an earlier timepoint for each type of lesion and IGA **Treatment Success** will be performed only if superiority (one-sided p<=0.025) is seen at the later timepoint.	Modified as per FDA suggestion
11.1 Monitoring	Monitoring visits will **apply** place . . .	Monitoring visits will **take** place	Correction
	. . . Sponsor . . .	. . . Sponsor or **Sponsor's representative .** . .	Multiple corrections

a) Old Table 3 – IGA Scale

Table 3: IGA Scale for Acne Vulgaris

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions present; rare **(eg, <5)** non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some noninflammatory lesions are present; few **(eg, <10)** inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	**Many noninflammatory lesions**; multiple **(eg, between 25 and 40)** inflammatory lesions **present**; many papules/pustules; there may or may not be a few nodulocystic lesions
4	Severe	Inflammatory lesions predominate, many papules/pustules **(eg, between 40 and 75**); there may be a few nodulocystic lesions
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

b) New Table 3 – IGA Scale

Table 3: IGA Scale for Acne Vulgaris

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions may be present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink- red)
2	Mild	Some noninflammatory lesions are present, **with** few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	**Many noninflammatory 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
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

c) Inserted in Section 10.2

Another consideration for the sample size must be given to the secondary endpoint of noninflammatory lesions which will be compared to the vehicle for non-inferiority. The margin for non-inferiority will be 30% of the change from baseline to week 12. In a phase 2 study, change from baseline in noninflammatory lesions at week 9 was 22.8 for the vehicle group with a standard deviation of 18. Assuming approximately the same reduction at week 12, a 30% non-inferiority margin is about 6.8 lesions. The following table provides approximate sample sizes for alternate assumptions for 90% power to show non-inferiority.

Vehicle mean noninflammatory lesion reduction	Minocycline 4% foam mean noninflammatory lesion reduction	Sample sizes (vehicle, active)
CCI	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI

If Minocycline 4% foam has the same effect on noninflammatory lesions as vehicle, CCI subjects on vehicle and CCI on 4% foam will be needed for 90% power to show non-inferiority. If Minocycline 4% foam has a slightly less effect on noninflammatory lesions (CCI lesion reduction versus CCI in vehicle), there will be about 90% power to show non-inferiority.

16.2.2. Amendment 2, effective April 6, 2016

The following is the summary of the changes that were made to Protocol FX2014-05 Version 2 issued February 26, 2016.

Section	Revision		Rationale
	Old Text	**New Text**	
5.2 Exclusion Criteria	2. Dermatological condition of the face or facial hair (eg, beard, sideburns, mustache) that could interfere with the clinical evaluations	2. **Acne conglobata, acne fulminans, secondary acne (chloracne, drug induced acne) or any dermatological condition**.	Specific exclusions added for clarity
6. Study Procedures Table 1: Schedule of Procedures	Urine pregnancy test (females, only)	Urine pregnancy test (females **of childbearing potential** only)	Clarification
	Inserted	**"X"** for pregnancy tests to be performed at **Week 3, 6 and 9**	Modified per FDA
	Inserted	New line and "**X**" for Subject Satisfaction Questionnaire for Week 12	Procedure added
Footnote 3	. . . **This visit and** the procedures required at this visit can be combined with Screening. . .	. . . The procedures required at **these visits** can be combined . . .	Clarification

Section	Revision		Rationale
	Old Text	**New Text**	
Footnote 6	Home pregnancy tests will be dispensed to all female subjects at risk of becoming pregnant and will be performed whenever there is a suspicion of pregnancy (e.g., a missed period)	**Perform urine pregnancy test at indicated visits. Also dispense home urine pregnancy test at Week 12 if subject is continuing into open-label treatment**	Modified per FDA
6.1.2. Baseline Visit, Visit 1	. . . **This visit and** the procedures required at this visit can be combined with Screening. . .	. . . The procedures required at **this visit** can be combined with Screening . . .	Clarification
	Perform urine pregnancy test	Perform urine pregnancy test **in females of childbearing potential**	Clarification
6.1.4. Visit 3, Week 3; 6.1.5. Visit 4, Week 6; 6.1.6. Visit 5, Week 9	Inserted	**Perform urine pregnancy test in females of childbearing potential**	Modified per FDA
6.1.7. Visit 6, Week 12	Collect a urine sample from female subjects for a urine pregnancy test	**Perform urine pregnancy test in females of childbearing potential**	Clarification
	Inserted	• **Administer Subject Satisfaction Questionnaire**	Procedure added
	• If subject is continuing . . . dispense 1 kit (2 canisters) of FMX-101 . . .	• If subject is continuing . . . dispense **2 kits (4 canisters)** of FMX-101 .	Correction
6.2 Part 2 – Open-label Table 4: Schedule of Procedures	Inserted	"**X**" for pregnancy tests to be dispensed at Weeks 16, 22, 28, 34, 40 and 46.	Modified per FDA
	Inserted	New line and "**X**" for Subject Satisfaction Questionnaire for Week 52	Procedure added
Footnote 3	Home pregnancy tests will be dispensed to all female subjects at risk of becoming pregnant whenever . . .	Home pregnancy tests will be dispensed **at each visit** to all **female subjects of childbearing potential** and will be performed at least **monthly and** whenever . . . **Perform urine pregnancy test at Final Visit.**	Modified per FDA

Section	Revision		Rationale
	Old Text	**New Text**	
6.2.1. Visit 7, Week 16	Inserted	**Dispense Home pregnancy kit to all female subjects of childbearing potential**	Modified per FDA
6.2.2. Visits 8 – 12, Weeks 22 - 46	Inserted	**Dispense Home pregnancy kit to all female subjects of childbearing potential**	Modified per FDA
6.2.3. Visit 13, Final Visit – Week 52	Collect a urine sample from female subjects for a urine pregnancy test	**Perform urine pregnancy test in females of childbearing potential**	Clarification
	Inserted	• **Administer Subject Satisfaction Questionnaire**	Procedure added
7.1.3.1. Part 1 – Double-blind	After shaking . . . , a small amount of foam should be expressed . . . . additional amounts of foam should also be applied . . .approximately the same time each day preferably in the evening.	After shaking . . .a small amount of foam **(about 1/2 gram or a cherry-sized amount)** should be expressed . . . additional amounts **(up to a total of 4g)** of foam should also be applied . . .the same time each day preferably in the evening **at bedtime**.	Clarification of amounts and timing
8.3. Subject Satisfaction Questionnaire	Inserted	**A satisfaction questionnaire will be administered at Visit 6, Week 12 and Visit 13, Week 52 (see Section 16.1, Appendix 1).**	Procedure added
9.6. Clinical Laboratory Tests	Serum chemistry, hematology and urinalysis will be evaluated at Baseline, Week 12 and Final Visit.	Serum chemistry, hematology and urinalysis will be evaluated at Baseline, Week 12/ Final Visit **of the double-blind phase of the Study, and at Week 28 and Week 52/Final Visit of the open-label phase of the Study**.	Modified per FDA

Section	Revision		Rationale
	Old Text	**New Text**	
9.6.1. Urine Pregnancy Test	A urine sample will be collected from all female subjects for a urine pregnancy test at Baseline, Week 12 and Final Visit or when a subject prematurely withdraws from the study.	A urine **pregnancy test will be performed on all females of childbearing potential at Baseline, Week 3, Week 6, Week 9 and Week 12 of the double-blind phase of the Study** and Final Visit or when a subject prematurely withdraws from the study. **Home pregnancy kits will be provided at each visit to all female subjects of childbearing potential in the open-label phase of the Study and are to be used at least monthly and if a pregnancy is suspected between visits (e.g., if a subject misses a period). A urine pregnancy test will be performed at Week 52/ Final Visit.**	Modified per FDA
9.7.1. Tolerability	. . pigmentation . . .	. . .**hyper**pigmentation . . .	Correction
9.8.4. Adverse Event Follow-up	Adverse events that are ongoing when a subject withdraws from or completes the study will be followed until resolution or stabilization (in the opinion of the Investigator), or for 30 days, whichever is shorter.	Adverse events, **and tolerability signs and symptoms greater than zero (0),** that are ongoing when a subject withdraws from or completes the study will be followed until resolution or stabilization (in the opinion of the Investigator), or for 30 days, whichever is shorter.	Modified as per FDA suggestion

Section	Revision		Rationale
	Old Text	**New Text**	
9.8.4.1. Pregnancy reporting	A urine pregnancy test will be performed . . . at Baseline and Week 12/Final Visit of the double-blind phase of the Study or when a subject prematurely withdraws . . .	A urine pregnancy test will be performed . . .at Baseline, **Week 3, Week 6, Week 9** and Week 12/Final Visit of the double-blind phase of the Study or when a subject prematurely withdraws . . .	Modified as per FDA suggestion
	Home pregnancy kits will be provided to all female subjects at risk of becoming pregnant and are to be used if a pregnancy is suspected between visits (e.g., if a subject misses a period).	Home pregnancy kits will be provided to all female subjects **of childbearing potential in the open-label phase of the Study** and are to be used **at least monthly and** if a pregnancy is suspected between visits (e.g., if a subject misses a period). A urine pregnancy test will be performed at Final Visit.	
10.3 Analysis Populations	• Have not been compliant with the dosing regimen (ie, subjects missed more than 5 consecutive days of dosing and took less than 80% of expected doses)	• Have not, **in the opinion of the investigator, been compliant with the treatment regimen (e.g. reported frequent missed doses)**	Modify definition of Per Protocol Population
10.6.3 Efficacy Analysis	Non-inferiority margin is defined as 40% of the noninflammatory lesion reduction in the vehicle group at Week 12	Non-inferiority margin is defined as **30%** of the noninflammatory lesion reduction in the vehicle group at Week 12	Correction
16.1. Appendix 1 – Subjects Satisfaction Questionnaire	Inserted	See **Appendix 1** (p.52)	Procedure added