An Open-Label Study to Evaluate the Long-Term Safety of Topical Administration of FMX103 for 40 weeks in the Treatment of Moderate to Severe Facial Papulopustular Rosacea (Study FX2016-13)

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Date of Protocol: 22 June 2017

CLINICAL PROTOCOL

Title Page

Study Title:	An Open-Label Study to Evaluate the Long-Term Safety of Topical Administration of FMX103 for 40 weeks in the Treatment of Moderate to Severe Facial Papulopustular Rosacea (Study FX2016-13)
Sponsor:	Foamix Pharmaceuticals, Inc. 520 US Highway 22, Suite 305 Bridgewater, NJ 08807
Protocol Identification:	FX2016-13
Product:	FMX103 1.5% minocycline foam
Indication Studied:	Papulopustular Rosacea
Study Phase:	3
Sponsor's Signatory:	PPD
GCP Statement:	This study will be conducted in accordance with Good Clinical Practice. Essential documents will be archived according to CPMP/ICH/135/95
Date of Protocol:	22 June 2017
Version of Protocol	Version 2 (Amendment 1)
Supercedes:	Version 1, issued 06 March 2017
Prepared by:	The Write Company, LLC

Signature Page

Title: An Open-Label Study to Evaluate the Long-Term Safety of Topical Administration of FMX103 for 40 weeks in the Treatment of Moderate to Severe Facial Papulopustular Rosacea (Study FX2016-13)

CONFIDENTIAL

Project Number: FMX103

Foamix Department	Name/Title		Date
CLINICAL DEVELOPMENT	PPD	PPD	PPD
REGULATORY AFFAIRS	PPD	PPD	PPD

Synopsis

Name of Sponsor/Company: Foamix Pharmaceuticals, Inc.	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: FMX103	**Volume:**	
Name of Active Ingredient: Minocycline hydrochloride	**Page:**	
Title of Study:	An Open-Label Study to Evaluate the Long-Term Safety of Topical Administration of FMX103 for 40 weeks in the Treatment of Moderate to Severe Facial Papulopustular Rosacea (Study FX2016-13)	
Protocol No:	FX2016-13	
Study Centers:	Multicenter (approximately 80 sites in the USA)	
Publication (reference):	None	
Primary Objective:	The primary objective is to show that open-label extended treatment with FMX103 1.5%, for up to an additional 40 weeks, is safe and well tolerated.	
Study Design and Methods:	This is an open-label, multicenter, 40-week extension study to evaluate the long-term safety, tolerability, and efficacy of FMX103 1.5% topical foam in the treatment of moderate-to-severe facial papulopustular rosacea. Subjects entering this study will have recently participated in 1 of 2 pivotal, double-blind, vehicle-controlled, safety and efficacy studies (FX2016-11 and FX2016-12). Subjects must demonstrate that they are eligible to continue into Study FX2016-13 based in part on safety evaluations performed at Visit 5/Week 12 (Final Visit) of one of the previous double-blind studies. In addition, the subject's Investigator's Global Assessment (IGA) at Visit 5/Week 12 (Final Visit) should not have worsened relative to the subject's IGA at Day 0/Baseline of one of the previous double-blind studies. At the completion of Visit 5/Week 12 (Final Visit) in Study FX2016-11 or Study FX2016-12, subjects may be invited to continue into this open-label study for an additional 40 weeks of open-label treatment. A minimum of 400 subjects will be enrolled into from Studies FX2016-11 and FX2016-12. Subjects who elect to continue into this open-label study will receive supplies of active FMX103 1.5% minocycline foam. Treatment during the open-label study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment if there is clinical improvement or resolution of rosacea. Even if the treatment is suspended temporarily, the subject will continue in the study and will attend all scheduled clinic visits. If at any time the rosacea recurs or worsens, treatment 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. Baseline of Study FX2016-13 will occur on the same day as Visit 5/Week 12 (Final Visit) of either Study FX2016-11 or Study FX2016-12. Subsequent visits for this open-label study will occur at Weeks 4, 10, 16, 22, 28, 34, and 40, during which safety and efficacy evaluations will be performed. Week 40 is the Final Visit (Visit 7) of this study. A safety follow-up telephone call will occur 4 weeks after Final Visit (Visit 7).
Number of Subjects (planned):	The planned minimum enrollment is a minimum of 400 male and female subjects who were previously enrolled in Study FX2016-11 or Study FX2016-12. The sample size is intended to ensure that at least 300 subjects continue to self-administer the study drug as needed for at least 6 months and 100 subjects continue for at least 1 year (ie, combined duration of treatment between the double-blind and open-label studies). The number of subjects at each site will be determined by the rate of recruitment in Studies FX2016-11 and FX2016-12. No statistical rationale for subject number is provided.
Diagnosis and Main Criteria for Inclusion:	Healthy male or non-pregnant females, aged ≥18 years, who had a clinical diagnosis of moderate to severe facial papulopustular rosacea at the start of the previous double-blind study who completed 12 weeks of double-blind treatment in Study FX2016-11 or Study FX2016-12; are willing to continue on open-label treatment with FMX103 in the current study and do not have a worsening of disease, determined by IGA, at Visit 5/Week 12 (Final Visit) relative to the Day 0/Baseline assessment of the previous study.
Test Product, Dose and Mode of Administration:	FMX103 minocycline foam 1.5%. Topical application, self-administered dosing as needed, for up to 40 weeks.
Reference Therapy:	Not applicable.
Study Duration:	Subject participation in the study will be up to 44 weeks.
Endpoints and Outcomes:	**Safety Evaluations** The safety assessments will include adverse events (volunteered, observed, and elicited by general questioning in a non-suggestive manner); clinical laboratory tests; vital signs; physical examinations; and local signs and symptom assessments of the skin at the application sites (including erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation scores). **Efficacy Evaluations** The efficacy parameters will include inflammatory lesion counts and IGA at Baseline and at Weeks 4, 10, 16, 22, 28, 34, and 40 (Final Visit).

Statistical Methods:	The All-Treated population, defined as all subjects who use the study drug at least once, will be used for all analyses. Missing data will not be imputed. All analyses will be based on observed data. The primary endpoints are the absolute change in the inflammatory lesion count compared to Baseline and the dichotomized IGA score, where success is defined as a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Week 40 compared to Baseline. The secondary endpoints of change from Baseline of Study FX2016-11 and Study FX2016-12 to each visit in inflammatory lesion count, IGA treatment success and a Subject Satisfaction Questionnaire administered at Visit 7 (Week 40/Final Visit) will also be summarized. No statistical tests will be performed for any of the endpoints. The safety and tolerability safety of topical minocycline foam applied as needed for an additional 40 weeks will be evaluated using summary statistics and individual subject data listings. No statistical tests will be performed for any of the safety assessments.

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartic acid transaminase
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CRF	Case report form
CRO	Contract Research Organization
eCRF	Electronic case report form
FV	Final Visit
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
OC	Observed cases
OTC	Over-the-counter
PT	Preferred term
RBC	Red blood cell
RDC	Remote data capture
SAE	Serious adverse event
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
US	United States
WBC	White blood cell

2 STUDY ADMINISTRATIVE STRUCTURE

Internal

Name	Affiliation / Address / Telephone Number	Responsibility
PPD		
PPD PPD PPD PPD PPD	Foamix Pharmaceuticals, Inc. 520 US Highway 22 Bridgewater, NJ 08807	Sponsor

External – Contract Research Organization (CRO)

Name	Affiliation / Address / Telephone Number	Responsibility
Premier Research	Research Triangle Park One Park Drive, STE 150 PO Box 13608 Research Triangle Park, NC 27709 Tel: 512-686-1256 FMX103Medical@premier-research.com	Medical Monitor

3 INTRODUCTION

Papulopustular rosacea is a chronic disorder affecting both the skin and eyes. It is a syndrome of undetermined etiology characterized by both vascular and papulopustular components involving the face and occasionally the neck and upper trunk. Clinical findings are usually limited to the sun exposed areas of the face and chest and include mid-facial erythema, telangiectasia, papules and pustules, and sebaceous gland hypertrophy. Rosacea is characterized by episodic flushing of affected areas, which may be associated with consumption of alcohol, hot drinks, or spicy foods. During inflammatory episodes, affected areas of the skin, primarily the convexities of the face, develop swelling, papules, and pustules.

Rosacea occurs most commonly in adult life, between the ages of 30 and 60 years. It is very common in the United States (US) and Europe. Ocular involvement occurs in more than 50% of patients.

Mainstays of treatment for papulopustular rosacea are the oral tetracyclines: doxycycline and minocycline. Systemic doxycycline (Oracea®, doxycycline 40 mg capsules) is approved. Topical treatments for rosacea include metronidazole, azelaic acid, and brimonidine tartrate.

Minocycline hydrochloride is an established broad-spectrum antibiotic that is used orally "off-label" in the treatment of papulopustular rosacea. Foamix has developed a topical minocycline foam product that is being evaluated for the treatment of papulopustular rosacea. The study medication FMX103 (minocycline HCl 1.5% foam) facilitates easy application and even distribution of the agent, thereby improving treatment convenience.

The efficacy and safety of FMX103 have been established in a Phase 2 study in 232 adult subjects with moderate to severe papulopustular rosacea (Study FX2015-10).

The purpose of this Phase 3 open-label extension study is to evaluate the long-term safety, tolerability, and efficacy of topical FMX103 1.5% (minocycline foam) during a 40-week period of self-administered dosing as needed in subjects with moderate to severe facial papulopustular rosacea who have previously participated in 1 of 2 Phase 3, 12-week, double-blind, vehicle-controlled safety and efficacy studies: Studies FX2016-11 and FX2016-12.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective is to show that open-label extended treatment with FMX103 1.5%, for up to an additional 40 weeks, is safe and well tolerated.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is an open-label, multicenter, 40-week extension study to evaluate the long-term safety, tolerability, and efficacy of FMX103 1.5% topical foam in the treatment of moderate to severe facial papulopustular rosacea. Subjects will be eligible to enter this study upon successful

completion of 1 of 2 pivotal, double-blind, vehicle-controlled, safety and efficacy Phase 3 studies (FX2016-11 and FX2016-12) and if they meet all of the entry criteria.

At the completion of Visit 5/Week 12 (Final Visit, or FV) in Study FX2016-11 or Study FX2016-12, subjects who meet entry criteria will be invited to continue into this open-label study for an additional 40 weeks of treatment. A minimum of 400 subjects from Studies FX2016-11 and FX2016-12 will be enrolled into open-label Study FX2016-13. Subsequent enrollment of additional subjects will be considered as necessary to meet regulatory requirements. Subjects who elect to continue into this open-label study will receive supplies of active FMX103 1.5% minocycline foam.

Treatment during the open-label study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment of some or all facial areas if there is clinical improvement or resolution of the rosacea in those areas. Even if the treatment is partially or completely suspended temporarily, the subject will continue in the study and will attend all scheduled clinic visits. If at any time their rosacea 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.

Baseline of Study FX2016-13 will occur on the same day as Visit 5/Week 12 (Final Visit) of either Study FX2016-11 or Study FX2016-12. Subsequent visits for the open-label study will occur at Weeks 4, 10, 16, 22, 28, 34, and 40, during which safety and efficacy evaluations will be performed. Week 40 is the Final Visit (Visit 7) of this study.

Safety and efficacy evaluations will be performed as shown in Table 1.

5.2 Rationale for Study Design and Dose Selection

Chronic exposure in an open-label design is appropriate to evaluate the safety of long-term use. The omission of a control group is appropriate. Subjects will be selected according to pre-defined entry criteria from 2 pivotal, Phase 3, randomized, multicenter, double-blind, vehicle-controlled, 12-week studies. The open-label study treatment duration of 40 weeks will thus result in a total treatment duration of 52 weeks, adequate for chronic exposure.

This open-label extension study is necessary to obtain safety information about the long-term use of FMX103 1.5% to treat facial papulopustular rosacea because of its chronic nature. The study design is expected to provide sufficient safety information to fulfill the International Conference on Harmonization (ICH) E1 guideline.

The concentration of minocycline (1.5%) was selected according to formulation integrity and stability considerations and based on the results of the Phase 2 Study FX2015-10.

6 STUDY POPULATION

The study population will be comprised of subjects who have completed Study FX2016-11 or Study FX2016-12 and have agreed and are eligible to continue into this 40-week open-label extension study. A minimum of 400 subjects will be enrolled at approximately 80 sites in the US. All subjects will receive active treatment with FMX103 1.5% minocycline foam.

6.1 Inclusion Criteria

Subjects will be included in the study if they meet all of the following inclusion criteria at the time of enrollment:

1. Healthy male or non-pregnant females, aged ≥18 years, who had a clinical diagnosis of moderate to severe facial papulopustular rosacea at the start of the previous double-blind study (Study FX2016-11 or Study FX2016-12).
2. Have completed and signed an appropriately administered informed consent form (ICF) prior to any study-related procedures.
3. Have completed 12 weeks of treatment in either Study FX2016-11 or Study FX2016-12.
4. Have not had a worsening of disease, determined by the Investigator's Global Assessment (IGA), at Visit 5/Week 12 (Final Visit) relative to the Day 0/Baseline assessment in Study FX2016-11 or Study FX2016-12.
5. Are willing to continue on open-label treatment with FMX103 as described in this protocol.
6. If a woman of child-bearing potential, have a negative urine pregnancy test and agree to use an effective method of contraception (Section 8.8). A sterile sexual partner is NOT considered an adequate form of birth control.
7. If a woman of child-bearing potential 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 of the study.

6.2 Exclusion Criteria

Subjects will be excluded from enrollment in the study for any of the following reasons:

1. Women who are pregnant, lactating, or planning to become pregnant during the study.
2. Have a new systemic disease or condition, including an ongoing AE that might interfere with the conduct of the study or the interpretation of results.
3. Have developed a condition that would have been exclusionary for Study FX2016-11 or Study FX2016-12, including pseudomembranous colitis, antibiotic-associated colitis, hepatitis, liver damage, renal impairment, drug addiction, or alcohol abuse.
4. Have abnormal laboratory values at the Final Visit (Week 12) of Study FX2016-11 or Study FX2016-12 that are considered clinically significant. Subjects are permitted to enroll in the study whilst laboratory results for Final Visit (Week 12) for Study FX2016-11 or Study FX2016-12 are pending receipt.
5. Are unable to fully comply with the study requirements.

7 STUDY PROCEDURES

The schedule of study assessments and procedures is presented in Table 1. If a subject withdraws from the study prematurely, he or she should return to the study site for an early termination

visit, during which all evaluations described under Visit 7/Week 40 (Final Visit) should be performed.

Table 1 Schedule of Study Assessments and Procedures – Study FX2016-13

Assessment or Procedure	Baseline[a]	Visits						Final Visit[b]	Safety Follow-up[c]
Study Visit	**(FV of previous DB Study)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**N/A**
Study Week (Week since beginning of previous DB study)	**1 (12)**	**4 (16)**	**10 (22)**	**16 (28)**	**22 (34)**	**28 (40)**	**34 (46)**	**40 (52)**	**44 (56)**
Informed consent	X								
Record subject identification[d]	X								
Inclusion/exclusion criteria	X								
Physical examination (including weight)	X							X	
Blood pressure/heart rate[e]	X	X	X	X	X	X	X	X	
Blood/urine samples for clinical laboratory tests	X			X				X	
Urine pregnancy test[f]	X	X	X	X	X	X	X	X	
Investigator's Global Assessment	X[g]	X	X	X	X	X	X	X	
Lesion counts	X	X	X	X	X	X	X	X	
Subject Satisfaction Questionnaire								X	
Local signs and symptom assessments[h]	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Perform drug accountability		X	X	X	X	X	X	X	
Collect used drug canister(s)		X	X	X	X	X	X	X	
Dispense study drug	X	X	X	X	X	X	X		
Review application instructions	X	X	X	X	X	X	X		
Schedule/confirm next visit or call (for safety follow-up only)	X	X	X	X	X	X	X	X	

DB = double-blind; FV = final visit; N/A = not applicable, no visit

a. Baseline for the study will be conducted at the same time as Visit 5/Week 12 (Final Visit) of Study FX2016-11 or Study FX2016-12. All assessments performed at Visit 5/Week 12 (Final Visit) of Study FX2016-11 or Study FX2016-12 should not be repeated but should be recorded as the same assessments at Baseline for this study.

b. If a subject withdraws from the study prematurely, all evaluations described under Visit 7/Week 40 (Final Visit) should be performed.

c. A safety follow-up telephone call will be made 4 weeks after Visit 7/Week 40 (Final Visit).

d. Previously assigned subject identification from Study FX2016-11 or Study FX2016-12 will be used in this study.

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

f. A urine pregnancy test will be done at the study site at every visit for all subjects of childbearing potential; home pregnancy tests will be dispensed at each visit, if needed, and will be performed at least monthly or whenever there is a suspicion of pregnancy (eg, a missed menstrual period).

g. The subject's Investigator's Global Assessment (IGA) at Visit 5/Week 12 (Final Visit) should not have worsened relative to the subject's IGA at Day 0/Baseline of one of the previous double-blind studies.

h. The severity of each of the following local rosacea signs/symptoms will be measured: erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation.

7.1 Baseline (also Visit 5/Week 12 [Final Visit] of previous double-blind study)

- Obtain a signed and dated ICF.
- Record subject identification from Study FX2016-11 or Study FX2016-12.
- Assess eligibility according to the inclusion (Section 6.1) and exclusion criteria (Section 6.2).
- Record physical examination results, including weight, from Final Visit (Section 10.3).
- Record blood pressure and heart rate results from Final Visit (Section 10.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test and dispense a home pregnancy test kit (Section 10.4.1).
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 10.4.2).
- Perform IGA (Section 9.1.2).
- Perform facial lesion count of inflammatory lesions (Section 9.1.1).
- Perform local signs and symptom assessments (Section 10.5.1).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.6).
- Review application instructions to confirm that the subject continues to use the study drug properly.
- Dispense 1 study drug kits (ie, 2 canisters) of FMX103 1.5%.
- Dispense facial cleanser and moisturizer.
- Schedule/confirm the next study visit.

7.2 Visits 1 through 6, Weeks 4, 10, 16, 22, 28, and 34 (±5 days)

- Measure blood pressure and heart rate (Section 10.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test and dispense a home pregnancy test kit as needed (Section 10.4.1).
- **At Visit 3 (Week 16) only** – Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 10.4.2).
- Perform IGA (Section 9.1.2).
- Perform facial lesion count of inflammatory lesions (Section 9.1.1).
- Perform local signs and symptom assessments (Section 10.5.1).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.6).

- Review application instructions to confirm that the subject continues to use study drug properly.
- Collect used study drug canister(s).
- Perform drug accountability.
- Dispense 2 study drug kits (ie, 4 canisters) of FMX103 1.5% if required.
- Confirm that subject continues to use only the provided facial cleanser and moisturizer and dispense additional quantities as required.
- Schedule/confirm the next study visit.

7.3 Visit 7, Week 40/Final Visit (±5 days) or Early Termination

- Perform physical examination, including weight (Section 10.3).
- Measure blood pressure and heart rate (Section 10.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test (Section 10.4.1).
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 10.4.2).
- Perform IGA (Section 9.1.2).
- Perform facial lesion count of inflammatory lesions (Section 9.1.1).
- Have the subject complete the Subject Satisfaction Questionnaire (Section 9.2.2).
- Perform local signs and symptom assessments (Section 10.5.1).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.6).
- Collect used study drug canister(s).
- Perform drug accountability.
- Schedule/confirm a safety follow-up telephone call 4 weeks from Visit 7/Week 40 if required (Section 7.4).

7.4 Safety Follow-Up (±5 days)

A safety follow-up telephone call will be made 4 weeks after Visit 7/Week 40 (Final Visit). Follow up on adverse events and any new concomitant medications will be recorded.

8 STUDY TREATMENTS

This is an open-label study; all subjects will receive FMX103 1.5% minocycline foam.

8.1 Treatment Administered

The description of study drug kits and treatment is shown in Table 2.

Table 2 Study Drug Kits and Treatment – Study FX2016-13

Dosage form description:	Foam containing minocycline HCl 1.5%
Package description:	2 canisters of FMX103 1.5%, each canister containing 35 g of the clinical trial supply foam
Daily dose:	As needed application of a sufficient amount of foam to cover the whole face. Estimated maximum is 0.5 g of drug product containing 7.5 mg (1.5% active) of minocycline.
Cumulative maximal dose over 40 weeks:	Up to approximately 2100 mg of minocycline assuming application of 0.5 g of FMX103 1.5% foam once daily to the face for 280 days.
Dispensing:	Up to 2 kits consisting of 2 canisters/kit (ie, 4 canisters total) dispensed at Baseline and Visits 1-6 (Weeks 4-34). Up to a total of 14 kits (28 canisters) dispensed to the subject for the study.

8.1.1 Dosing Instructions

At enrollment, subjects will receive supplies of active FMX103 1.5% minocycline foam.

Up to 2 study drug kits consisting of 2 canisters/kit (ie, 4 canisters total of investigational drug) will be dispensed at Baseline and Visits 1 through 6 (Weeks 4 through 34). Subjects will be instructed to express a small amount of study drug from the canister onto the finger tips and then apply as a thin layer over the whole face. Additional drug may be used as needed to assure the entire face is treated. Sufficient product will be dispensed at each visit to allow continuation of treatment as required.

Study drug should be applied at approximately the same time each day, about 1 hour before bedtime.

Treatment during this open-label study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment if there is clinical improvement or resolution of rosacea. Even if treatment is suspended temporarily, the subject will continue in the study and will attend all scheduled clinic visits. If at any time the rosacea recurs or worsens, treatment 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.

8.1.2 Manufacturer

The manufacturer of the investigational product is CCI [redacted]

8.1.3 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, as follow:
    - "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.

8.1.4 Storage of Study Drug

FMX103 1.5% canisters must be stored at 2°C – 8°C until being dispensed to the subject. Subsequently, the canisters 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.

8.2 Study Drug Accountability

The Investigator will have overall responsibility for 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 Response Technology (IRT) 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 and each canister that has been retrieved from a 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 IRT to assign and dispense kits to the subjects. Reasons for digression from the expected dispensing regimen must also be recorded.

8.3 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 canisters 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.

8.4 Method of Assignment of Study Drug

After clinical evaluations and all other Baseline procedures have been completed, authorized site personnel will acknowledge that the applicable subject meets all the specified inclusion criteria (Section 6.1) and none of the exclusion criteria (Section 6.2). All subjects who enroll into the open-label study will receive FMX103 1.5% minocycline foam as described in Section 8.1.1.

8.5 Selection and Timing of Doses in the Study

The 1.5% concentration of minocycline once daily has been shown to be effective compared to vehicle in a Phase 2 study in subjects with rosacea. The once-daily dosing regimen is also appropriate given the pharmacokinetic characteristics of topical minocycline.

8.6 Blinding

Not applicable.

8.7 Prior/Concomitant Therapy

Subjects should use the facial cleanser CCI [redacted] and the facial moisturizer CCI [redacted]. Both products will be provided by the Sponsor. Alternative, non-medicated cleansers or moisturizers may be used if agreed to by the Sponsor.

Prior therapy is defined as medications, either prescription or over the counter (OTC), used prior to and/or concomitantly during participation in Study FX2016-11 or Study FX2016-12.

The use of or change in the dose of any concomitant medications, either prescription or over the counter (OTC), 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. If a woman of child bearing potential 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 study.

If a subject is taking anticoagulant therapy, he or she should be advised that a downward adjustment of their anticoagulant dose may be required.

See the FMX103 investigator's brochure (IB) for information about tetracyclines and possible drug-drug interactions.

8.8 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/occlusion, or bilateral oophorectomy) or who 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 in the follow list 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 – (Oral 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
- Complete abstinence

8.9 Treatment Compliance

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

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

9 EFFICACY ASSESSMENTS

Every attempt must be made to ensure the same evaluator performs the efficacy evaluations for a particular subject throughout the study; when this is not possible, another approved evaluator may perform the evaluations. Following are the methods and scales that will be used to measure each of the efficacy parameters to be performed.

9.1 Primary Efficacy Assessments

The efficacy assessments will include the inflammatory lesion counts and the IGA of severity of disease and will be performed by the Investigator/evaluator.

9.1.1 Lesion Counts

The number of papules, pustules, and nodules will be counted and the numbers recorded. Facial area lesion counts will be made for the forehead, left and right cheeks, nose, and chin. The lesion counts performed at Visit 5/Week 12 [Final Visit] in Study FX2016-11 or Study FX2016-12) will constitute the Baseline value for this study. Lesion counts will be repeated at Visit 1 (Week 4), Visit 2 (Week 10), Visit 3 (Week 16), Visit 4 (Week 22), Visit 5 (Week 28), Visit 6 (Week 34), and Visit 7 (Week 40/Final Visit).

9.1.2 Investigator Global Assessment

The Investigator will also assess the global severity of rosacea using the IGA scale as described in Table 3. The IGA performed at Visit 5/Week 12 [Final Visit] in Study FX2016-11 or Study FX2016-12) will constitute the Baseline value for this study. Assessment will be repeated at Visit 1 (Week 4), Visit 2 (Week 10), Visit 3 (Week 16), Visit 4 (Week 22), Visit 5 (Week 28), Visit 6 (Week 34), and Visit 7 (Week 40/Final Visit).

Table 3 IGA Scale for Rosacea – Study FX2016-13

Score	Grade	Description
0	Clear	No inflammatory papules or pustules
1	Almost clear	Few inflammatory papules or pustules
2	Mild	Several inflammatory papules or pustules
3	Moderate	Moderate number of inflammatory papules or pustules and no nodules
4	Severe	Many inflammatory papules or pustules, and up to 2 nodules

9.2 Secondary Efficacy Assessments

9.2.1 Subject Satisfaction Questionnaire

A Subject Satisfaction Questionnaire (Appendix 1) will be administered at Visit 7 (Week 40/Final Visit).

10 SAFETY ASSESSMENTS

The safety assessments in this study are standard safety measures in clinical studies, including the monitoring of AEs (volunteered, observed, and elicited by general questioning in a non-suggestive manner), clinical laboratory tests, vital signs, physical examinations, and local signs and symptom assessments (including erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation) scores.

10.1 Concomitant Medications

All medications that the subject is currently taking or any change in medication or dosage since the last visit will be documented throughout the study. The reason for use or change of dose of a concomitant therapy may need to be reported as an AE.

10.2 Vital Signs

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

10.3 Physical Examination

A complete physical examination (excluding the genitourinary examination), including body weight, will be performed at Baseline (ie, Visit 5/Week 12 [Final Visit] in Study FX2016-11 or Study FX2016-12) and at Visit 7 (Week 40/Final Visit).

10.4 Clinical Laboratory Tests

Serum chemistry, hematology and urinalysis will be evaluated at Baseline (ie, Visit 5/Week 12 [Final Visit] in Study FX2016-11 or Study FX2016-12) and at Visit 3 (Week 16) and Visit 7 (Week 40/Final Visit). All clinical laboratory tests will be analyzed by a central laboratory. Table 4 presents the specific clinical laboratory tests to be evaluated.

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

Table 4 Clinical Laboratory Tests – Study FX2016-13

Hematology	Urinalysis	Serum chemistry
Hematocrit	Bilirubin	Alanine aminotransferase (ALT)
Hemoglobin	Blood	Albumin
Platelet count	Glucose	Alkaline phosphatase
Red blood cell (RBC) count	Ketones	Aspartic acid transaminase (AST)
White blood cell (WBC) count with differential	Leukocytes esterase	Blood urea nitrogen (BUN)
	pH	Calcium
	Protein	Chloride
	Specific gravity	Cholesterol
		Creatinine
		Creatinine kinase
	Urine pregnancy test performed at the site	Gamma glutamyl transferase (GGT)
		Globulin
		Glucose
		Phosphorus
		Potassium
		Sodium
		Total bilirubin (if elevated obtain direct bilirubin)
		Total protein
		Uric acid

10.4.1 Urine Pregnancy Test

A urine pregnancy test will be performed at the study site on all females of childbearing potential at all study visits and when a subject withdraws from the study prematurely. In addition, home pregnancy tests will be dispensed at each study visit to all female subjects of a childbearing potential and will be performed at least monthly and whenever there is a suspicion of pregnancy (eg, a missed or late menstrual period).

10.4.2 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 sites must be equipped to store the samples according to the laboratory manual procedures before shipping to the central laboratory.

10.5 Other Safety Measurements

10.5.1 Local Signs and Symptom Assessments

Local signs and symptom assessments of the skin at the application sites measured at Visit 5/Week 12 [Final Visit] in Study FX2016-11 or Study FX2016-12) will constitute Baseline values for this study. Assessments will be repeated at Visit 1 (Week 4), Visit 2 (Week 10), Visit 3 (Week 16), Visit 4 (Week 22), Visit 5 (Week 28), Visit 6 (Week 34), and Visit 7 (Week 40/Final Visit). The following local signs and symptoms will be measured: erythema, telangiectasia,

burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation. The score for signs will be determined by the Investigator and must represent the subject's condition at the time of the evaluation; the score for symptoms (ie, burning/stinging, flushing/blushing) should be scored based on the subject's symptoms reported for the previous 3 days.

These signs/symptoms should not be included as AEs, unless a sign/symptom is believed to have been related to the study drug or is the reason for discontinuation from the study.

10.5.1.1 Erythema (Clinical Erythema Assessment Scale)

Erythema of the face will be graded according to the following scale:

- 0 = clear skin/no signs of erythema
- 1 = almost clear of erythema, slight redness
- 2 = mild erythema, definite redness
- 3 = moderate erythema, marked redness
- 4 = severe erythema, fiery redness

10.5.1.2 Telangiectasia

The severity of facial telangiectasia will be graded according to the following scale:

- 0 = None
- 1 = Mild: scattered telangiectasia
- 2 = Moderate: numerous telangiectasia
- 3 = Severe: dense telangiectasia forming sprays of vessels

10.5.1.3 Burning/Stinging

The severity of facial burning/stinging will be graded according to the following scale:

- 0 = None: no warm or burning sensation
- 1 = Mild: slight warm tingling/stinging sensation; not really bothersome
- 2 = Moderate: constant or intermittent warm tingling/stinging sensation that is somewhat bothersome
- 3 = Severe: bothersome warm to hot tingling/stinging sensation

10.5.1.4 Flushing/Blushing

The severity of facial flushing/blushing will be graded according to the following scale:

- 0 = None
- 1 = Mild: sporadic episodes lasting for a few moments to several minutes
- 2 = Moderate: intermittent episodes lasting for greater than 30 minutes
- 3 = Severe: almost constant episodes lasting for several hours

10.5.1.5 Dryness/Xerosis

The severity of facial dryness/xerosis will be graded according to the following scale:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe

10.5.1.6 Itching

The severity of facial itching will be graded according to the following scale:

- 0 = None
- 1 = Mild: sporadic itching lasting for a few moments to several minutes
- 2 = Moderate: intermittent itching lasting for greater than 30 minutes
- 3 = Severe: almost constant, intense itching lasting for several hours

10.5.1.7 Peeling/Desquamation

The severity of facial peeling/desquamation will be graded according to the following scale:

- 0 = No peeling
- 1 = Mild: small, scattered areas of scaling/flaking
- 2 = Moderate: larger, contiguous areas of scaling/flaking
- 3 = Severe: pronounced flaking/shedding scales covering entire application area

10.5.1.8 Hyperpigmentation

The severity of facial skin hyperpigmentation will be graded according to the following scale:

- 0 = None
- 1 = Mild: few scattered, small areas of light hyperpigmentation
- 2 = Moderate: larger or more intense areas of hyperpigmentation
- 3 = Severe: intense, extensive hyperpigmentation

10.6 Adverse Events

10.6.1 Method of Determining Adverse Events

Safety assessments will include recording AEs reported spontaneously by the subject or observed by the Investigator. Adverse events will be recorded at each visit on the appropriate case report form (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 separately.

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 OTC)
- Were admitted to a hospital or had any accidents
- Developed unusual headaches or changes in vision

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

When an AE is suspected, all relevant evaluations will be performed and appropriate treatment provided. Additional follow-up will be done as necessary (Section 10.6.4) 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 10.6.2 and Section 10.6.3, respectively.

10.6.2 Adverse Event Definitions

10.6.2.1 Adverse Events

An AE is any unfavorable or unintended sign, symptom, or disease that appears or worsens in a subject after the subject signs the ICF 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 (Note: 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.

10.6.2.2 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) event.

  (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.

10.6.2.3 Severity of Adverse Events

The severity of an AE refers to the extent to which it 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.

10.6.2.4 Relationship of Adverse Events to Study Treatments

Causality refers to the relationship of the AE to the 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.

10.6.2.5 Adverse Events Expectedness

Expected AEs are defined as those described in the FMX103 IB. If an event increases in intensity or severity from that described in the IB, it will be considered unexpected.

10.6.3 Reporting Adverse Events

Adverse events that occur from the time of informed consent 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.

Any SAEs occurring in a subject receiving study drug must be reported to the Sponsor 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 done by faxing the completed SAE Report Form to the Sponsor. Any pertinent follow-up information should be provided in a similar manner. Contact information is provided below:

Foamix Pharmaceuticals Inc./Premier Research

Pharmacovigilance

Phone: +1 215-282-5434

Fax: +1 215-972-8765

Email: globalPv-US@premier-research.com

10.6.4 Adverse Event Follow-up

Adverse events that are ongoing when a subject withdraws from or completes the study will be followed until they resolve or the subject stabilizes (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, the subject is stable, or the event is 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 they resolve or the subject is stable.

10.6.4.1 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 ICF that the subject signs must document this discussion.

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

Urine pregnancy tests will be performed on all females of childbearing potential as described in Section 10.4.1.

During the study, all female subjects of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, positive home pregnancy test [Section 10.4.1], missed or late menstrual period, etc.). 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 site pregnancy testing are available. The Sponsor and site monitor must be notified and relevant information collected on the appropriate 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); pregnancy will not be captured as an AE.

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

10.6.5 Clinically Significantly Abnormal Laboratory Results

All laboratory values that are outside of the normal range for that parameter will be flagged when reported to the site. The Investigator will determine which out-of-range laboratory test results should be characterized as clinically significant and 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.

10.7 Appropriateness of Safety Measurement

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

11 STATISTICAL DESIGN AND ANALYSIS

11.1 Statistical Analysis Plan

A detailed statistical analysis plan will be finalized prior to database lock.

Descriptive statistics for qualitative variables (eg, race) will include the number and percentage of subjects with the qualitative response. Missing responses will be enumerated; however, 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, and minimum and maximum values.

11.2 Determination of Sample Size

The planned minimum enrollment is 400 male and female subjects who were previously enrolled in Study FX2016-11 or Study FX2016-12. The sample size is intended to ensure that at least 300 subjects continue to self-administer the study drug as needed for at least 6 months and 100 subjects continue for at least 1 year (ie, combined duration of treatment between the double-blind and open-label studies). The number of subjects at each site will be determined by the rate of recruitment in Studies FX2016-11 and FX2016-12. No statistical rationale for subject number is provided.

11.3 Analysis Populations

The following populations are defined for analysis:

- The All-Treated population: all subjects who use study drug at least once. This population will be used for safety and efficacy analyses.

11.4 Subject Accounting, Demographics, and Baseline Characteristics

Demographics, baseline characteristics, medical and surgical history (FX2016-11 and FX2016-12) and prior and concomitant medications will be summarized. Study completion status and reasons for discontinuation will also be displayed.

11.5 Efficacy Endpoints

11.5.1 Primary Efficacy Endpoints

The primary efficacy endpoints are:

- The absolute change in the inflammatory lesion count at Week 40 compared to Baseline.
- The dichotomized IGA score where success is defined as a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Week 40 compared to Baseline.

For the efficacy analyses, Baseline will be defined as Day 0/Baseline of the initial double-blind study, ie either Study FX2016-11 or Study FX2016-12. The changes from Baseline of Studies FX2016-11 and FX2016-12 to Week 40 of this study for each of the primary endpoints will be calculated. Descriptive statistics (number of subjects, mean, median, standard error, coefficient of variation, minimum and maximum) for each variable will be presented for each visit and for the changes from Baseline. No hypothesis testing will be performed.

11.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The absolute change from Day 0/Baseline in the inflammatory lesion count at Weeks 4, 10, 16, 22, 28 and 34.

- The dichotomized IGA score where success is defined as a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Weeks 4, 10, 16, 22, 28 and 34 compared to Day 0/Baseline.
- The percent change in inflammatory lesion count at Weeks 4, 10, 16, 22, 28 and 34 compared to Day 0/Baseline.
- The Subject Satisfaction Questionnaire administered at Visit 7 (Week 40/Final Visit).

11.6 Safety Endpoints

Safety endpoints will be reported on the All Treated population. Safety assessments will be summarized in tables using descriptive statistics and in individual by-subject listings. No statistical tests will be performed for any of the safety assessments. For the safety analyses, Baseline will be defined as Day 0/Baseline of the initial double-blind study, ie either Study FX2016-11 or Study FX2016-12.

Treatment-emergent AEs (TEAEs) will be defined as events that emerge having been absent prior to enrollment in this study or worsen relative to the pre-enrollment state. Summaries of AEs will be limited to TEAEs. The number and percentage of subjects reporting events under each System Organ Class (SOC) and preferred term (PT) will be summarized. At each level of summarization, a subject will be counted only once if he or she reported one or more events. The severity of TEAEs and relationship to the study drug will be summarized in a similar manner. For summaries of relationship to the 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. All TEAEs continuing, but not worsening, after enrollment in this study will also be tabulated.

Treatment-emergent AEs, vital signs, physical examination assessments and clinical laboratory measurements will be summarized using descriptive statistics. For vital signs, change from Baseline values will also be summarized. For all safety variables, subject data listings will be provided.

11.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) terminology will be used to classify all AEs with respect to SOC and PT.

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

11.6.2 Local Signs and Symptoms Assessments

Local signs and symptom assessments will include active assessments of erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation using the scales described under Section 10.5.1. Local signs and symptom assessments will be summarized using descriptive statistics at Baseline and at each post-Baseline time point. Changes from Baseline will also be summarized.

11.6.3 Clinical Laboratory Results

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 treatment-emergent clinically significant abnormal laboratory values will be presented for each treatment group. Clinical significance is based on the Investigator's judgment.

11.7 Interim Analysis

No interim analysis is planned.

12 STUDY MANAGEMENT

12.1 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 institutional review board (IRB) to have direct access to all documents pertaining to the study. The Investigator is to notify the Sponsor immediately 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 Good Clinical Practice (GCP)-ICH, and their agreement with the source data. The monitor will also verify the correct use of the study drug. At 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 clinical research associate, as needed, regarding study concerns and/or questions. Contact information is provided in the Study Reference Manual for the site.

12.2 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.

12.3 Protocol Deviations

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

12.4 Withdrawal of Subjects

Subjects or Investigators may choose to discontinue a subject's participation in the study at any time. Subjects may be withdrawn from the study because of any 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 10.6.4.
- **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 the subject is stable to the satisfaction of the Investigator in consultation with the medical monitor.
- **Lost to Follow-up:** Confirmed at minimum by two phone calls and a traceable letter without answer.
- **Subject Request:** Subject requests, for any reason (eg, AE), to be withdrawn or withdraws his or her consent.
- **Protocol Deviation:** 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, subject's relocation, etc. If a subject becomes pregnant during the study, she will be withdrawn from the study and followed through conclusion of the pregnancy (Section 10.6.4.1).

If a subject is withdrawn from the study following the start of study drug, all Visit 7 (Week 40/Final Visit) assessments should be completed. Subjects withdrawn from the study will not be replaced.

12.5 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.

12.6 Publication Policy

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

13 ETHICS

13.1 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.

13.2 Institutional Review Boards

This protocol (and any changes), all consent 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 physician-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 take place followed by IRB approval. Review and approval by the IRB for continuation of the study must take place at least once a year.

13.3 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 or 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 or she is willing to sign a statement of informed consent. Only subjects who voluntarily sign the ICF may enter the study.

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

The original signed ICF will remain in the Investigator's files. The Investigator or designee will indicate in each subject's source documents that he or she has informed the subject about the study and its procedures, the subject has signed and dated the ICF, 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 subject's willingness to continue in the study.

13.4 Subject Confidentiality

The Sponsor will ensure 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.

The investigative site assigns a unique subject identification code 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.

13.5 Records Retention

The Investigator must maintain essential study documents (protocol and amendments, source documentation corresponding to all information contained in the CRFs, signed ICF 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.

13.6 Financing

Funding for this study will be agreed upon 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 1 year after the completion of the study.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and the Investigator will take 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 Department may conduct periodic audits of the study processes, including, but not limited to, auditing the clinical site, laboratories, vendors and contract research organizations CROs, the clinical database, and the final study report.

15 DATA HANDLING AND RECORD KEEPING

This study will use web-based, 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 eCRFs 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 username and password. Only the person who owns the username and password will enter the system using that username 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 remote data capture (RDC) system 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 and approval 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.

16 REFERENCE LIST

Not applicable.

17 STUDY AMENDMENTS

This section describes the amendment(s) that have been made to the protocol for Study FX2016-13.

Section 17.1 describes the changes made to Protocol FX2016-13 Version 1 issued March 6th, 2017, via Amendment 1 effective June 22nd, 2017.

17.1 Amendment 1, effective June 22nd, 2017

The following is the summary of the changes that were made to Protocol FX2016-11 Version 1 issued March 6th, 2017.

Content changes:

New or changed text is **bolded.**

Section(s)	Revision		Rationale
	Old Text	New Text	
Section 2 Study Administrative Structure	PPD	**Premier Research**	Removal of study team member due to retirement.
Synopsis (Statistical Methods)	Change from baseline of Study FX2016-11 and Study FX2016-12 to each visit from inflammatory lesion count and IGA will also be summarized. The secondary endpoint is the Subject Satisfaction Questionnaire administered at Visit 7 (Week 40/Final Visit).	The secondary endpoints of change from Baseline of Study FX2016-11 and Study FX2016-12 to each visit in inflammatory lesion count, IGA treatment success and a Subject Satisfaction Questionnaire administered at Visit 7 (Week 40/Final Visit) will also be summarized.	Clarification of study secondary efficacy endpoints and their statistical treatment.
Section 6.3 Exclusion Criteria 4	None.	**Subjects are permitted to enroll in the study whilst laboratory results for Final Visit (Week 12) for Study FX2016-11 or Study FX2016-12 are pending receipt.**	Clarification of subject study qualification status while laboratory results are pending receipt.

Section(s)	Revision		Rationale
	Old Text	New Text	
Table 1 Schedule of Study Assessments and Procedures – Study FX2016-13, Footnote f	A urine pregnancy test will be done at the study site at every visit for all subjects of childbearing potential; home pregnancy tests will be dispensed at each visit and will be performed at least monthly or whenever there is a suspicion of pregnancy (eg, a missed period).	A urine pregnancy test will be done at the study site at every visit for all subjects of childbearing potential; home pregnancy tests will be dispensed at each visit**, if needed,** and will be performed at least monthly or whenever there is a suspicion of pregnancy (eg, a missed **menstrual** period).	Home pregnancy tests will be dispensed as needed and not necessarily at every visit.
Section 7.1 Baseline (also Visit 5/Week 12 [Final Visit] of previous double-blind study)	Have the subject complete the Subject Global Assessment (Section 9.2.1). Have the subject complete the Subject Satisfaction Questionnaire (Section 9.2.2).	Text removed.	Typographical error.
Section 7.2 Visits 1 through 6, Weeks 4, 10, 16, 22, 28, and 34 (±5 days)	…and dispense a home pregnancy test kit (Section 10.4.1).	…and dispense a home pregnancy test kit **as needed** (Section 10.4.1).	Home pregnancy tests will be dispensed as needed and not necessarily at every visit.
Section 7.2 Visits 1 through 6, Weeks 4, 10, 16, 22, 28, and 34 (±5 days)	Dispense a home pregnancy test kit (Section 10.4.1).	Text removed.	Repetition from previous bullet-point.

Section(s)	Revision		Rationale
	Old Text	New Text	
Synopsis (Study Design and Methods), Table 1 footnote c., Section 7.4 Safety Follow-up (±5 days).	A safety follow-up telephone call will be made 4 weeks after Visit 7/Week 40 (Final Visit) for only those subjects who presented with either new or on-going adverse events at Visit 7/Week 40 (Final Visit). Follow up on these adverse events…	A safety follow-up telephone call will be made 4 weeks after Visit 7/Week 40. Follow up on adverse events…	Removal of qualifiers for safety follow-up.
Synopsis (Study Design and Methods), Table 2, Section 8.1.1 Dosing Instructions	…involved areas (of the face)…	…whole (entire) face…	Alignment with treatment area text within FX2016-11 and FX2016-12.
Table 2, Section 8.1.1 Dosing Instructions	…canister containing 25 g of the clinical…	canister containing **3**5 g of the clinical…	Correction of unit pack size.
Section 8.1.1 Dosing Instructions	None.	Study drug should be applied at approximately the same time each day, about 1 hour before bedtime.	Alignment with treatment application text within FX2016-11 and FX2016-12.

Section(s)	Revision		Rationale
	Old Text	New Text	
Section 11.5.2 Secondary Efficacy Endpoints	New text.	**The secondary efficacy endpoints are:** **The absolute change from Day 0/Baseline in the inflammatory lesion count at Weeks 4, 10, 16, 22, 28 and 34.** **The dichotomized IGA score where success is defined as a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Weeks 4, 10, 16, 22, 28 and 34 compared to Day 0/Baseline.** **The percent change in inflammatory lesion count at Weeks 4, 10, 16, 22, 28 and 34 compared to Day 0/Baseline.**	Addition of secondary efficacy endpoints.
Section 11.6 Safety Endpoints	New text.	**For the safety analyses, Baseline will be defined as Day 0/Baseline of the initial double-blind study, ie either Study FX2016-11 or Study FX2016-12.**	Clarification of Baseline timepoint for safety analyses.
Section 11.6 Safety Endpoints	Treatment-emergent AEs, vital signs, and clinical laboratory measurements…	Treatment-emergent AEs, vital signs, **physical examination assessments** and clinical laboratory measurements…	Section incorrectly placed.

Section(s)	Revision		Rationale
	Old Text	New Text	
Section 11.6 Safety Endpoints	Local signs and symptom assessments will include active assessments of erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation using the scales described under Section 10.5.1.	Text removed to Section 11.6.2.	As above.
Section 11.6.2 Local Signs and Symptoms Assessments	Vital sign and physical examination parameters will be summarized using descriptive statistics at Baseline and at each post-Baseline timepoint. Changes from Baseline will also be summarized.	Local signs and symptom assessments will include active assessments of erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation using the scales described under Section 10.5.1.	As above.
Section 11.6.3	Baseline is defined as the last non-missing value prior to enrollment in this study.	Text removed.	Baseline has been defined within Section 11.6.

APPENDIX 1: Subject Satisfaction Questionnaire

The following 8 questions will be asked of the subject at Visit 7 (Week 40/Final Visit):

1. How satisfied are you with how easy this product is to use?
2. How satisfied are you with how this product feels on your skin after treatment?
3. How satisfied are you with the odor of this product after treatment?
4. How satisfied are you with the color of this product after treatment?
5. How satisfied are you with the ease of application of the product to your skin?
6. How satisfied are you with the ease in which this product fits into your daily routine?
7. How satisfied are you with this product compared to other products you have previously used for rosacea, such as gels and creams?
8. Overall, how likely are you to use this product with other rosacea treatments?
9. Overall, how likely are you to recommend this product to a friend?
10. Overall, how satisfied are you with this product?

Answers to Questions 1 through 9 will be selected from the following:

- 1 = Very Satisfied
- 2 = Satisfied
- 3 = Somewhat Satisfied
- 4 = Dissatisfied
- 5 = Very Dissatisfied

The answer to Questions 10 and 11 will be selected from the following:

- 1 = Very Likely
- 2 = Likely
- 3 = Somewhat Likely
- 4 = Unlikely
- 5 = Very Unlikely

APPENDIX 2: Acknowledgment Of Receipt And Review Of Protocol

Protocol Number: FX2016-13, Version 2

Protocol Title: An Open-Label Study to Evaluate the Long-Term Safety of Topical Administration of FMX103 for 40 weeks in the Treatment of Moderate to Severe Facial Papulopustular Rosacea (Study FX2016-13)

I hereby acknowledge receipt and review of the following Protocol:

1. Version 2, dated June 22nd, 2017

_____

Principal Investigator Name (Print)

_____ _____

Principal Investigator Signature | Date of Signature (DD MMM YYYY)

CLINICAL PROTOCOL

Title Page

Study Title:	An Open-Label Study to Evaluate the Long-Term Safety of Topical Administration of FMX103 for 40 weeks in the Treatment of Moderate to Severe Facial Papulopustular Rosacea (Study FX2016-13)
Sponsor:	Foamix Pharmaceuticals, Inc. 520 US Highway 22, Suite 305 Bridgewater, NJ 08807
Protocol Identification:	FX2016-13
Product:	FMX103 1.5% minocycline foam
Indication Studied:	Papulopustular Rosacea
Study Phase:	3
Sponsor's Signatory:	PPD
GCP Statement:	This study will be conducted in accordance with Good Clinical Practice. Essential documents will be archived according to CPMP/ICH/135/95
Date of Protocol:	06 Mar 2017
Version of Protocol	1
Supercedes:	None
Prepared by:	The Write Company, LLC

Signature Page

Title: An Open-Label Study to Evaluate the Long-Term Safety of Topical Administration of FMX103 for 40 weeks in the Treatment of Moderate to Severe Facial Papulopustular Rosacea (Study FX2016-13)

CONFIDENTIAL

Project Number: FMX103

Foamix Department	Name/Title	Signature	Date
CLINICAL DEVELOPMENT	PPD	PPD	PPD
REGULATORY AFFAIRS	PPD	PPD	PPD

Synopsis

Name of Sponsor/Company: Foamix Pharmaceuticals, Inc.	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: FMX103	**Volume:**	
Name of Active Ingredient: Minocycline hydrochloride	**Page:**	
Title of Study:	An Open-Label Study to Evaluate the Long-Term Safety of Topical Administration of FMX103 for 40 weeks in the Treatment of Moderate to Severe Facial Papulopustular Rosacea (Study FX2016-13)	
Protocol No:	FX2016-13	
Study Centers:	Multicenter (approximately 80 sites in the USA)	
Publication (reference):	None	
Primary Objective:	The primary objective is to show that open-label extended treatment with FMX103 1.5%, for up to an additional 40 weeks, is safe and well tolerated.	
Study Design and Methods:	This is an open-label, multicenter, 40-week extension study to evaluate the long-term safety, tolerability, and efficacy of FMX103 1.5% topical foam in the treatment of moderate-to-severe facial papulopustular rosacea. Subjects entering this study will have recently participated in 1 of 2 pivotal, double-blind, vehicle-controlled, safety and efficacy studies (FX2016-11 and FX2016-12). At Baseline, subjects must demonstrate that they are eligible to continue into Study FX2016-13 based in part on safety evaluations performed at Visit 5/Week 12 (Final Visit) of one of the previous double-blind studies. In addition, the subject's Investigator's Global Assessment (IGA) at Visit 5/Week 12 (Final Visit) should not have worsened relative to the subject's IGA at Day 0/Baseline of one of the previous double-blind studies. At the completion of Visit 5/Week 12 (Final Visit) in Study FX2016-11 or Study FX2016-12, subjects may be invited to continue into this open-label study for an additional 40 weeks of open-label treatment. A minimum of 400 subjects will be enrolled into from Studies FX2016-11 and FX2016-12. Subjects who elect to continue into this open-label study will receive supplies of active FMX103 1.5% minocycline foam. Treatment during the open-label study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment of some or all facial areas if there is clinical improvement or resolution of the rosacea in those areas. Even if the treatment is partially or completely suspended temporarily, the subject will continue in the study and will attend all scheduled clinic visits. If at any time the	

	rosacea 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. Baseline of Study FX2016-13 will occur on the same day as Visit 5/Week 12 (Final Visit) of either Study FX2016-11 or Study FX2016-12. Subsequent visits for this open-label study will occur at Weeks 4, 10, 16, 22, 28, 34, and 40, during which safety and efficacy evaluations will be performed. Week 40 is the Final Visit (Visit 7) of this study. A safety follow-up telephone call will occur 4 weeks after Final Visit (Visit 7) for only those subjects that present with new or on-going adverse events at Week 40 (Final Visit).
Number of Subjects (planned):	The planned minimum enrollment is a minimum of 400 male and female subjects who were previously enrolled in Study FX2016-11 or Study FX2016-12. The sample size is intended to ensure that at least 300 subjects continue to self-administer the study drug as needed for at least 6 months and 100 subjects continue for at least 1 year (ie, combined duration of treatment between the double-blind and open-label studies). The number of subjects at each site will be determined by the rate of recruitment in Studies FX2016-11 and FX2016-12. No statistical rationale for subject number is provided.
Diagnosis and Main Criteria for Inclusion:	Healthy male or non-pregnant females, aged ≥18 years, who had a clinical diagnosis of moderate to severe facial papulopustular rosacea at the start of the previous double-blind study who completed 12 weeks of double-blind treatment in Study FX2016-11 or Study FX2016-12; are willing to continue on open-label treatment with FMX103 in the current study and do not have a worsening of disease, determined by IGA, at Visit 5/Week 12 (Final Visit) relative to the Day 0/Baseline assessment of the previous study.
Test Product, Dose and Mode of Administration:	FMX103 minocycline foam 1.5%. Topical application, self-administered dosing as needed, for up to 40 weeks.
Reference Therapy:	Not applicable.
Study Duration:	Subject participation in the study will be up to 44 weeks.
Endpoints and Outcomes:	**Safety Evaluations** The safety assessments will include adverse events (volunteered, observed, and elicited by general questioning in a non-suggestive manner); clinical laboratory tests; vital signs; physical examinations; and local signs and symptom assessments of the skin at the application sites (including erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation scores). **Efficacy Evaluations** The efficacy parameters will include inflammatory lesion counts and IGA at Baseline and at Weeks 4, 10, 16, 22, 28, 34, and 40 (Final Visit).

Statistical Methods:	The All-Treated population, defined as all subjects who use the study drug at least once, will be used for all analyses. Missing data will not be imputed. All analyses will be based on observed data. The primary endpoints are the absolute change in the inflammatory lesion count compared to Baseline and the dichotomized IGA score, where success is defined as a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Week 40 compared to Baseline. Change from baseline of Study FX2016-11 and Study FX2016-12 to each visit from inflammatory lesion count and IGA will also be summarized. The secondary endpoint is the Subject Satisfaction Questionnaire administered at Visit 7 (Week 40/Final Visit). No statistical tests will be performed for any of the endpoints. The safety and tolerability safety of topical minocycline foam applied as needed for an additional 40 weeks will be evaluated using summary statistics and individual subject data listings. No statistical tests will be performed for any of the safety assessments.

Table of Contents

List of Tables

1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartic acid transaminase
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CRF	Case report form
CRO	Contract Research Organization
eCRF	Electronic case report form
FV	Final Visit
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
OC	Observed cases
OTC	Over-the-counter
PT	Preferred term
RBC	Red blood cell
RDC	Remote data capture
SAE	Serious adverse event
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
US	United States
WBC	White blood cell

2 STUDY ADMINISTRATIVE STRUCTURE

Internal

Name	Affiliation / Address / Telephone Number	Responsibility
PPD PPD PPD PPD PPD PPD	Foamix Pharmaceuticals, Inc. 520 US Highway 22 Bridgewater, NJ 08807	Sponsor

External – Contract Research Organization (CRO)

Name	Affiliation / Address / Telephone Number	Responsibility
PPD	Premier Research Research Triangle Park One Park Drive, STE 150 PO Box 13608 Research Triangle Park, NC 27709 Tel: 512-686-1256 FMX103Medical@premier-research.com	Medical Monitor

3 INTRODUCTION

Papulopustular rosacea is a chronic disorder affecting both the skin and eyes. It is a syndrome of undetermined etiology characterized by both vascular and papulopustular components involving the face and occasionally the neck and upper trunk. Clinical findings are usually limited to the sun exposed areas of the face and chest and include mid-facial erythema, telangiectasia, papules and pustules, and sebaceous gland hypertrophy. Rosacea is characterized by episodic flushing of affected areas, which may be associated with consumption of alcohol, hot drinks, or spicy foods. During inflammatory episodes, affected areas of the skin, primarily the convexities of the face, develop swelling, papules, and pustules.

Rosacea occurs most commonly in adult life, between the ages of 30 and 60 years. It is very common in the United States (US) and Europe. Ocular involvement occurs in more than 50% of patients.

Mainstays of treatment for papulopustular rosacea are the oral tetracyclines: doxycycline and minocycline. Systemic doxycycline (Oracea®, doxycycline 40 mg capsules) is approved. Topical treatments for rosacea include metronidazole, azelaic acid, and brimonidine tartrate.

Minocycline hydrochloride is an established broad-spectrum antibiotic that is used orally "off-label" in the treatment of papulopustular rosacea. Foamix has developed a topical minocycline foam product that is being evaluated for the treatment of papulopustular rosacea. The study medication FMX103 (minocycline HCl 1.5% foam) facilitates easy application and even distribution of the agent, thereby improving treatment convenience.

The efficacy and safety of FMX103 have been established in a Phase 2 study in 232 adult subjects with moderate to severe papulopustular rosacea (Study FX2015-10).

The purpose of this Phase 3 open-label extension study is to evaluate the long-term safety, tolerability, and efficacy of topical FMX103 1.5% (minocycline foam) during a 40-week period of self-administered dosing as needed in subjects with moderate to severe facial papulopustular rosacea who have previously participated in 1 of 2 Phase 3, 12-week, double-blind, vehicle-controlled safety and efficacy studies: Studies FX2016-11 and FX2016-12.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective is to show that open-label extended treatment with FMX103 1.5%, for up to an additional 40 weeks, is safe and well tolerated.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is an open-label, multicenter, 40-week extension study to evaluate the long-term safety, tolerability, and efficacy of FMX103 1.5% topical foam in the treatment of moderate to severe facial papulopustular rosacea. Subjects will be eligible to enter this study upon successful

completion of 1 of 2 pivotal, double-blind, vehicle-controlled, safety and efficacy Phase 3 studies (FX2016-11 and FX2016-12) and if they meet all of the entry criteria.

At the completion of Visit 5/Week 12 (Final Visit, or FV) in Study FX2016-11 or Study FX2016-12, subjects who meet entry criteria will be invited to continue into this open-label study for an additional 40 weeks of treatment. A minimum of 400 subjects from Studies FX2016-11 and FX2016-12 will be enrolled into open-label Study FX2016-13. Subsequent enrollment of additional subjects will be considered as necessary to meet regulatory requirements. Subjects who elect to continue into this open-label study will receive supplies of active FMX103 1.5% minocycline foam.

Treatment during the open-label study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment of some or all facial areas if there is clinical improvement or resolution of the rosacea in those areas. Even if the treatment is partially or completely suspended temporarily, the subject will continue in the study and will attend all scheduled clinic visits. If at any time their rosacea 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.

Baseline of Study FX2016-13 will occur on the same day as Visit 5/Week 12 (Final Visit) of either Study FX2016-11 or Study FX2016-12. Subsequent visits for the open-label study will occur at Weeks 4, 10, 16, 22, 28, 34, and 40, during which safety and efficacy evaluations will be performed. Week 40 is the Final Visit (Visit 7) of this study.

Safety and efficacy evaluations will be performed as shown in Table 1.

5.2 Rationale for Study Design and Dose Selection

Chronic exposure in an open-label design is appropriate to evaluate the safety of long-term use. The omission of a control group is appropriate. Subjects will be selected according to pre-defined entry criteria from 2 pivotal, Phase 3, randomized, multicenter, double-blind, vehicle-controlled, 12-week studies. The open-label study treatment duration of 40 weeks will thus result in a total treatment duration of 52 weeks, adequate for chronic exposure.

This open-label extension study is necessary to obtain safety information about the long-term use of FMX103 1.5% to treat facial papulopustular rosacea because of its chronic nature. The study design is expected to provide sufficient safety information to fulfill the International Conference on Harmonization (ICH) E1 guideline.

The concentration of minocycline (1.5%) was selected according to formulation integrity and stability considerations and based on the results of the Phase 2 Study FX2015-10.

6 STUDY POPULATION

The study population will be comprised of subjects who have completed Study FX2016-11 or Study FX2016-12 and have agreed and are eligible to continue into this 40-week open-label extension study. A minimum of 400 subjects will be enrolled at approximately 80 sites in the US. All subjects will receive active treatment with FMX103 1.5% minocycline foam.

6.1 Inclusion Criteria

Subjects will be included in the study if they meet all of the following inclusion criteria at the time of enrollment:

1. Healthy male or non-pregnant females, aged ≥18 years, who had a clinical diagnosis of moderate to severe facial papulopustular rosacea at the start of the previous double-blind study (Study FX2016-11 or Study FX2016-12).
2. Have completed and signed an appropriately administered informed consent form (ICF) prior to any study-related procedures.
3. Have completed 12 weeks of treatment in either Study FX2016-11 or Study FX2016-12.
4. Have not had a worsening of disease, determined by the Investigator's Global Assessment (IGA), at Visit 5/Week 12 (Final Visit) relative to the Day 0/Baseline assessment in Study FX2016-11 or Study FX2016-12.
5. Are willing to continue on open-label treatment with FMX103 as described in this protocol.
6. If a woman of child-bearing potential, have a negative urine pregnancy test and agree to use an effective method of contraception (Section 8.8). A sterile sexual partner is NOT considered an adequate form of birth control.
7. If a woman of child-bearing potential 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 of the study.

6.2 Exclusion Criteria

Subjects will be excluded from enrollment in the study for any of the following reasons:

1. Women who are pregnant, lactating, or planning to become pregnant during the study.
2. Have a new systemic disease or condition, including an ongoing AE that might interfere with the conduct of the study or the interpretation of results.
3. Have developed a condition that would have been exclusionary for Study FX2016-11 or Study FX2016-12, including pseudomembranous colitis, antibiotic-associated colitis, hepatitis, liver damage, renal impairment, drug addiction, or alcohol abuse.
4. Have abnormal laboratory values at the Final Visit (Week 12) of Study FX2016-11 or Study FX2016-12 that are considered clinically significant.
5. Are unable to fully comply with the study requirements.

7 STUDY PROCEDURES

The schedule of study assessments and procedures is presented in Table 1. If a subject withdraws from the study prematurely, he or she should return to the study site for an early termination visit, during which all evaluations described under Visit 7/Week 40 (Final Visit) should be performed.

Table 1 Schedule of Study Assessments and Procedures – Study FX2016-13

Assessment or Procedure	Baseline[a]	Visits						Final Visit[b]	Safety Follow-up[c]
Study Visit	**(FV of previous DB Study)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**N/A**
Study Week (Week since beginning of previous DB study)	**1 (12)**	**4 (16)**	**10 (22)**	**16 (28)**	**22 (34)**	**28 (40)**	**34 (46)**	**40 (52)**	**44 (56)**
Informed consent	X								
Record subject identification[d]	X								
Inclusion/exclusion criteria	X								
Physical examination (including weight)	X							X	
Blood pressure/heart rate[e]	X	X	X	X	X	X	X	X	
Blood/urine samples for clinical laboratory tests	X			X				X	
Urine pregnancy test[f]	X	X	X	X	X	X	X	X	
Lesion counts	X	X	X	X	X	X	X	X	
Investigator's Global Assessment	X[g]	X	X	X	X	X	X	X	
Subject Satisfaction Questionnaire								X	
Local signs and symptom assessments[h]	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Perform drug accountability		X	X	X	X	X	X	X	
Collect used drug canister(s)		X	X	X	X	X	X	X	
Dispense study drug	X	X	X	X	X	X	X		
Review application instructions	X	X	X	X	X	X	X		
Schedule/confirm next visit or call (for safety follow-up only)	X	X	X	X	X	X	X	X	

DB = double-blind; FV = final visit; N/A = not applicable, no visit

a. Baseline for the study will be conducted at the same time as Visit 5/Week 12 (Final Visit) of Study FX2016-11 or Study FX2016-12. All assessments performed at Visit 5/Week 12 (Final Visit) of Study FX2016-11 or Study FX2016-12 should not be repeated but should be recorded as the same assessments at Baseline for this study.

b. If a subject withdraws from the study prematurely, all evaluations described under Visit 7/Week 40 (Final Visit) should be performed.

c. A safety follow-up telephone call will be made 4 weeks after Visit 7/Week 40 (Final Visit) for those subjects who presented with either new or on-going adverse events at Visit 7/Week 40 (Final Visit).

d. Previously assigned subject identification from Study FX2016-11 or Study FX2016-12 will be used in this study.

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

f. A urine pregnancy test will be done at the study site at every visit for all subjects of childbearing potential; home pregnancy tests will be dispensed at each visit and will be performed at least monthly or whenever there is a suspicion of pregnancy (eg, a missed period).

g. The subject's Investigator's Global Assessment (IGA) at Visit 5/Week 12 (Final Visit) should not have worsened relative to the subject's IGA at Day 0/Baseline of one of the previous double-blind studies.

h. The severity of each of the following local rosacea signs/symptoms will be measured: erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation.

7.1 Baseline (also Visit 5/Week 12 [Final Visit] of previous double-blind study)

- Obtain a signed and dated ICF.
- Record subject identification from Study FX2016-11 or Study FX2016-12.
- Assess eligibility according to the inclusion (Section 6.1) and exclusion criteria (Section 6.2).
- Record physical examination results, including weight, from Final Visit (Section 10.3).
- Record blood pressure and heart rate results from Final Visit (Section 10.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test and dispense a home pregnancy test kit (Section 10.4.1).
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 10.4.2).
- Perform facial lesion count of inflammatory lesions (Section 9.1.1).
- Perform IGA (Section 9.1.2).
- Have the subject complete the Subject Global Assessment (Section 9.2.1).
- Have the subject complete the Subject Satisfaction Questionnaire (Section 9.2.2).
- Perform local signs and symptom assessments (Section 10.5.1).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.6).
- Review application instructions to confirm that the subject continues to use the study drug properly.
- Dispense 2 study drug kits (ie, 4 canisters) of FMX103 1.5%.
- Dispense facial cleanser and moisturizer.
- Schedule/confirm the next study visit.

7.2 Visits 1 through 6, Weeks 4, 10, 16, 22, 28, and 34 (±5 days)

- Measure blood pressure and heart rate (Section 10.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test and dispense a home pregnancy test kit (Section 10.4.1).
- Dispense a home pregnancy test kit (Section 10.4.1).
- **At Visit 3 (Week 16) only** – Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 10.4.2).
- Perform facial lesion count of inflammatory lesions (Section 9.1.1).
- Perform IGA (Section 9.1.2).

- Perform local signs and symptom assessments (Section 10.5.1).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.6).
- Review application instructions to confirm that the subject continues to use study drug properly.
- Collect used study drug canister(s).
- Perform drug accountability.
- Dispense 2 study drug kits (ie, 4 canisters) of FMX103 1.5% if required.
- Confirm that subject continues to use only the provided facial cleanser and moisturizer and dispense additional quantities as required.
- Schedule/confirm the next study visit.

7.3 Visit 7, Week 40/Final Visit (±5 days) or Early Termination

- Perform physical examination, including weight (Section 10.3).
- Measure blood pressure and heart rate (Section 10.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test (Section 10.4.1).
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 10.4.2).
- Perform facial lesion count of inflammatory lesions (Section 9.1.1).
- Perform IGA (Section 9.1.2).
- Have the subject complete the Subject Satisfaction Questionnaire (Section 9.2.2).
- Perform local signs and symptom assessments (Section 10.5.1).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.6).
- Collect used study drug canister(s).
- Perform drug accountability.
- Schedule/confirm a safety follow-up telephone call 4 weeks from Visit 7/Week 40 if required (Section 7.4).

7.4 Safety Follow-Up (±5 days)

A safety follow-up telephone call will be made 4 weeks after Visit 7/Week 40 (Final Visit) for only those subjects who presented with either new or on-going adverse events at Visit 7/Week 40

(Final Visit). Follow up on these adverse events and any new concomitant medications will be recorded.

8 STUDY TREATMENTS

This is an open-label study; all subjects will receive FMX103 1.5% minocycline foam.

8.1 Treatment Administered

The description of study drug kits and treatment is shown in Table 2.

Table 2 Study Drug Kits and Treatment – Study FX2016-13

Dosage form description:	Foam containing minocycline HCl 1.5%
Package description:	2 canisters of FMX103 1.5%, each canister containing 25 g of the clinical trial supply foam
Daily dose:	As needed application of a sufficient amount of foam to cover the involved area. Estimated maximum is 0.5 g of drug product containing 7.5 mg (1.5% active) of minocycline.
Cumulative maximal dose over 40 weeks:	Up to approximately 2100 mg of minocycline assuming application of 0.5 g of FMX103 1.5% foam once daily to the face for 280 days.
Dispensing:	Up to 2 kits consisting of 2 canisters/kit (ie, 4 canisters total) dispensed at Baseline and Visits 1-6 (Weeks 4-34). Up to a total of 14 kits (28 canisters) dispensed to the subject for the study.

8.1.1 Dosing Instructions

At enrollment, subjects will receive supplies of active FMX103 1.5% minocycline foam.

Up to 2 study drug kits consisting of 2 canisters/kit (ie, 4 canisters total of investigational drug) will be dispensed at Baseline and Visits 1 through 6 (Weeks 4 through 34). Subjects will be instructed to express a small amount of study drug from the canister onto the finger tips and then apply as a thin layer over all involved areas of the face as needed. Additional drug may be used as needed to assure the entire involved area is treated. Sufficient product will be dispensed at each visit to allow continuation of treatment as required.

Treatment during this open-label study will be guided by each subject's clinical response. The Investigator may elect to suspend treatment of some or all facial areas if there is clinical improvement or resolution of the rosacea in those areas. Even if the treatment is partially or completely suspended temporarily, the subject will continue in the study and will attend all scheduled clinic visits. If at any time the rosacea 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.

8.1.2 Manufacturer

The manufacturer of the investigational product is CCI [redacted]

8.1.3 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, as follow:
    - "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.

8.1.4 Storage of Study Drug

FMX103 1.5% canisters must be stored at 2°C – 8°C until being dispensed to the subject. Subsequently, the canisters 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.

8.2 Study Drug Accountability

The Investigator will have overall responsibility for 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 Response Technology (IRT) 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 and each canister that has been retrieved from a 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 IRT to assign and dispense kits to the subjects. Reasons for digression from the expected dispensing regimen must also be recorded.

8.3 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 canisters 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.

8.4 Method of Assignment of Study Drug

After clinical evaluations and all other Baseline procedures have been completed, authorized site personnel will acknowledge that the applicable subject meets all the specified inclusion criteria (Section 6.1) and none of the exclusion criteria (Section 6.2). All subjects who enroll into the open-label study will receive FMX103 1.5% minocycline foam as described in Section 8.1.1.

8.5 Selection and Timing of Doses in the Study

The 1.5% concentration of minocycline once daily has been shown to be effective compared to vehicle in a Phase 2 study in subjects with rosacea. The once-daily dosing regimen is also appropriate given the pharmacokinetic characteristics of topical minocycline.

8.6 Blinding

Not applicable.

8.7 Prior/Concomitant Therapy

Subjects should use the facial cleanser CCI [redacted] *r* and the facial moisturizer CCI [redacted] Both products will be provided by the Sponsor. Alternative, non-medicated cleansers or moisturizers may be used if agreed to by the Sponsor.

Prior therapy is defined as medications, either prescription or over the counter (OTC), used prior to and/or concomitantly during participation in Study FX2016-11 or Study FX2016-12.

The use of or change in the dose of any concomitant medications, either prescription or over the counter (OTC), 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. If a woman of child bearing potential 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 study.

If a subject is taking anticoagulant therapy, he or she should be advised that a downward adjustment of their anticoagulant dose may be required.

See the FMX103 investigator's brochure (IB) for information about tetracyclines and possible drug-drug interactions.

8.8 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/occlusion, or bilateral oophorectomy) or who 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 in the follow list 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 – (Oral 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
- Complete abstinence

8.9 Treatment Compliance

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

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

9 EFFICACY ASSESSMENTS

Every attempt must be made to ensure the same evaluator performs the efficacy evaluations for a particular subject throughout the study; when this is not possible, another approved evaluator may perform the evaluations. Following are the methods and scales that will be used to measure each of the efficacy parameters to be performed.

9.1 Primary Efficacy Assessments

The efficacy assessments will include the inflammatory lesion counts and the IGA of severity of disease and will be performed by the Investigator/evaluator.

9.1.1 Lesion Counts

The number of papules, pustules, and nodules will be counted and the numbers recorded. Facial area lesion counts will be made for the forehead, left and right cheeks, nose, and chin. The lesion counts performed at Visit 5/Week 12 [Final Visit] in Study FX2016-11 or Study FX2016-12) will constitute the Baseline value for this study. Lesion counts will be repeated at Visit 1 (Week 4), Visit 2 (Week 10), Visit 3 (Week 16), Visit 4 (Week 22), Visit 5 (Week 28), Visit 6 (Week 34), and Visit 7 (Week 40/Final Visit).

9.1.2 Investigator Global Assessment

The Investigator will also assess the global severity of rosacea using the IGA scale as described in Table 3. The IGA performed at Visit 5/Week 12 [Final Visit] in Study FX2016-11 or Study FX2016-12) will constitute the Baseline value for this study. Assessment will be repeated at Visit 1 (Week 4), Visit 2 (Week 10), Visit 3 (Week 16), Visit 4 (Week 22), Visit 5 (Week 28), Visit 6 (Week 34), and Visit 7 (Week 40/Final Visit).

Table 3 IGA Scale for Rosacea – Study FX2016-13

Score	Grade	Description
0	Clear	No inflammatory papules or pustules
1	Almost clear	Few inflammatory papules or pustules
2	Mild	Several inflammatory papules or pustules
3	Moderate	Moderate number of inflammatory papules or pustules and no nodules
4	Severe	Many inflammatory papules or pustules, and up to 2 nodules

9.2 Secondary Efficacy Assessments

9.2.1 Subject Satisfaction Questionnaire

A Subject Satisfaction Questionnaire (Appendix 1) will be administered at Visit 7 (Week 40/Final Visit).

10 SAFETY ASSESSMENTS

The safety assessments in this study are standard safety measures in clinical studies, including the monitoring of AEs (volunteered, observed, and elicited by general questioning in a non-suggestive manner), clinical laboratory tests, vital signs, physical examinations, and local signs and symptom assessments (including erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation) scores.

10.1 Concomitant Medications

All medications that the subject is currently taking or any change in medication or dosage since the last visit will be documented throughout the study. The reason for use or change of dose of a concomitant therapy may need to be reported as an AE.

10.2 Vital Signs

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

10.3 Physical Examination

A complete physical examination (excluding the genitourinary examination), including body weight, will be performed at Baseline (ie, Visit 5/Week 12 [Final Visit] in Study FX2016-11 or Study FX2016-12) and at Visit 7 (Week 40/Final Visit).

10.4 Clinical Laboratory Tests

Serum chemistry, hematology and urinalysis will be evaluated at Baseline (ie, Visit 5/Week 12 [Final Visit] in Study FX2016-11 or Study FX2016-12) and at Visit 3 (Week 16) and Visit 7 (Week 40/Final Visit). All clinical laboratory tests will be analyzed by a central laboratory. Table 4 presents the specific clinical laboratory tests to be evaluated.

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

Table 4 Clinical Laboratory Tests – Study FX2016-13

Hematology	Urinalysis	Serum chemistry
Hematocrit	Bilirubin	Alanine aminotransferase (ALT)
Hemoglobin	Blood	Albumin
Platelet count	Glucose	Alkaline phosphatase
Red blood cell (RBC) count	Ketones	Aspartic acid transaminase (AST)
White blood cell (WBC) count with differential	Leukocytes esterase	Blood urea nitrogen (BUN)
	pH	Calcium
	Protein	Chloride
	Specific gravity	Cholesterol
		Creatinine
		Creatinine kinase
	Urine pregnancy test performed at the site	Gamma glutamyl transferase (GGT)
		Globulin
		Glucose
		Phosphorus
		Potassium
		Sodium
		Total bilirubin (if elevated obtain direct bilirubin)
		Total protein
		Uric acid

10.4.1 Urine Pregnancy Test

A urine pregnancy test will be performed at the study site on all females of childbearing potential at all study visits and when a subject withdraws from the study prematurely. In addition, home pregnancy tests will be dispensed at each study visit to all female subjects of a childbearing potential and will be performed at least monthly and whenever there is a suspicion of pregnancy (eg, a missed or late menstrual period).

10.4.2 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 sites must be equipped to store the samples according to the laboratory manual procedures before shipping to the central laboratory.

10.5 Other Safety Measurements

10.5.1 Local Signs and Symptom Assessments

Local signs and symptom assessments of the skin at the application sites measured at Visit 5/Week 12 [Final Visit] in Study FX2016-11 or Study FX2016-12) will constitute Baseline values for this study. Assessments will be repeated at Visit 1 (Week 4), Visit 2 (Week 10), Visit 3 (Week 16), Visit 4 (Week 22), Visit 5 (Week 28), Visit 6 (Week 34), and Visit 7 (Week 40/Final Visit). The following local signs and symptoms will be measured: erythema, telangiectasia,

burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation. The score for signs will be determined by the Investigator and must represent the subject's condition at the time of the evaluation; the score for symptoms (ie, burning/stinging, flushing/blushing) should be scored based on the subject's symptoms reported for the previous 3 days.

These signs/symptoms should not be included as AEs, unless a sign/symptom is believed to have been related to the study drug or is the reason for discontinuation from the study.

10.5.1.1 Erythema (Clinical Erythema Assessment Scale)

Erythema of the face will be graded according to the following scale:

- 0 = clear skin/no signs of erythema
- 1 = almost clear of erythema, slight redness
- 2 = mild erythema, definite redness
- 3 = moderate erythema, marked redness
- 4 = severe erythema, fiery redness

10.5.1.2 Telangiectasia

The severity of facial telangiectasia will be graded according to the following scale:

- 0 = None
- 1 = Mild: scattered telangiectasia
- 2 = Moderate: numerous telangiectasia
- 3 = Severe: dense telangiectasia forming sprays of vessels

10.5.1.3 Burning/Stinging

The severity of facial burning/stinging will be graded according to the following scale:

- 0 = None: no warm or burning sensation
- 1 = Mild: slight warm tingling/stinging sensation; not really bothersome
- 2 = Moderate: constant or intermittent warm tingling/stinging sensation that is somewhat bothersome
- 3 = Severe: bothersome warm to hot tingling/stinging sensation

10.5.1.4 Flushing/Blushing

The severity of facial flushing/blushing will be graded according to the following scale:

- 0 = None
- 1 = Mild: sporadic episodes lasting for a few moments to several minutes
- 2 = Moderate: intermittent episodes lasting for greater than 30 minutes
- 3 = Severe: almost constant episodes lasting for several hours

10.5.1.5 Dryness/Xerosis

The severity of facial dryness/xerosis will be graded according to the following scale:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe

10.5.1.6 Itching

The severity of facial itching will be graded according to the following scale:

- 0 = None
- 1 = Mild: sporadic itching lasting for a few moments to several minutes
- 2 = Moderate: intermittent itching lasting for greater than 30 minutes
- 3 = Severe: almost constant, intense itching lasting for several hours

10.5.1.7 Peeling/Desquamation

The severity of facial peeling/desquamation will be graded according to the following scale:

- 0 = No peeling
- 1 = Mild: small, scattered areas of scaling/flaking
- 2 = Moderate: larger, contiguous areas of scaling/flaking
- 3 = Severe: pronounced flaking/shedding scales covering entire application area

10.5.1.8 Hyperpigmentation

The severity of facial skin hyperpigmentation will be graded according to the following scale:

- 0 = None
- 1 = Mild: few scattered, small areas of light hyperpigmentation
- 2 = Moderate: larger or more intense areas of hyperpigmentation
- 3 = Severe: intense, extensive hyperpigmentation

10.6 Adverse Events

10.6.1 Method of Determining Adverse Events

Safety assessments will include recording AEs reported spontaneously by the subject or observed by the Investigator. Adverse events will be recorded at each visit on the appropriate case report form (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 separately.

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 OTC)
- Were admitted to a hospital or had any accidents
- Developed unusual headaches or changes in vision

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

When an AE is suspected, all relevant evaluations will be performed and appropriate treatment provided. Additional follow-up will be done as necessary (Section 10.6.4) 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 10.6.2 and Section 10.6.3, respectively.

10.6.2 Adverse Event Definitions

10.6.2.1 Adverse Events

An AE is any unfavorable or unintended sign, symptom, or disease that appears or worsens in a subject after the subject signs the ICF 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 (Note: 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.

10.6.2.2 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) event.

  (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.

10.6.2.3 Severity of Adverse Events

The severity of an AE refers to the extent to which it 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.

10.6.2.4 Relationship of Adverse Events to Study Treatments

Causality refers to the relationship of the AE to the 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.

10.6.2.5 Adverse Events Expectedness

Expected AEs are defined as those described in the FMX103 IB. If an event increases in intensity or severity from that described in the IB, it will be considered unexpected.

10.6.3 Reporting Adverse Events

Adverse events that occur from the time of informed consent 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.

Any SAEs occurring in a subject receiving study drug must be reported to the Sponsor 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 done by faxing the completed SAE Report Form to the Sponsor. Any pertinent follow-up information should be provided in a similar manner. Contact information is provided below:

Foamix Pharmaceuticals Inc./Premier Research

Pharmacovigilance

Phone: +1 215-282-5434

Fax: +1 215-972-8765

Email: globalPv-US@premier-research.com

10.6.4 Adverse Event Follow-up

Adverse events that are ongoing when a subject withdraws from or completes the study will be followed until they resolve or the subject stabilizes (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, the subject is stable, or the event is 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 they resolve or the subject is stable.

10.6.4.1 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 ICF that the subject signs must document this discussion.

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

Urine pregnancy tests will be performed on all females of childbearing potential as described in Section 10.4.1.

During the study, all female subjects of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, positive home pregnancy test [Section 10.4.1], missed or late menstrual period, etc.). 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 site pregnancy testing are available. The Sponsor and site monitor must be notified and relevant information collected on the appropriate 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); pregnancy will not be captured as an AE.

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

10.6.5 Clinically Significantly Abnormal Laboratory Results

All laboratory values that are outside of the normal range for that parameter will be flagged when reported to the site. The Investigator will determine which out-of-range laboratory test results should be characterized as clinically significant and 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.

10.7 Appropriateness of Safety Measurement

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

11 STATISTICAL DESIGN AND ANALYSIS

11.1 Statistical Analysis Plan

A detailed statistical analysis plan will be finalized prior to database lock.

Descriptive statistics for qualitative variables (eg, race) will include the number and percentage of subjects with the qualitative response. Missing responses will be enumerated; however, 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, and minimum and maximum values.

11.2 Determination of Sample Size

The planned minimum enrollment is 400 male and female subjects who were previously enrolled in Study FX2016-11 or Study FX2016-12. The sample size is intended to ensure that at least 300 subjects continue to self-administer the study drug as needed for at least 6 months and 100 subjects continue for at least 1 year (ie, combined duration of treatment between the double-blind and open-label studies). The number of subjects at each site will be determined by the rate of recruitment in Studies FX2016-11 and FX2016-12. No statistical rationale for subject number is provided.

11.3 Analysis Populations

The following populations are defined for analysis:

- The All-Treated population: all subjects who use study drug at least once. This population will be used for safety and efficacy analyses.

11.4 Subject Accounting, Demographics, and Baseline Characteristics

Demographics, baseline characteristics, medical and surgical history (FX2016-11 and FX2016-12) and prior and concomitant medications will be summarized. Study completion status and reasons for discontinuation will also be displayed.

11.5 Efficacy Endpoints

11.5.1 Primary Efficacy Endpoints

The primary efficacy endpoints are:

- The absolute change in the inflammatory lesion count at Week 40 compared to Baseline.
- The dichotomized IGA score where success is defined as a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Week 40 compared to Baseline.

For the efficacy analyses, Baseline will be defined as Day 0/Baseline of the initial double-blind study, ie either Study FX2016-11 or Study FX2016-12. The changes from Baseline of Studies FX2016-11 and FX2016-12 to Week 40 of this study for each of the primary endpoints will be calculated. Descriptive statistics (number of subjects, mean, median, standard error, coefficient of variation, minimum and maximum) for each variable will be presented for each visit and for the changes from Baseline. No hypothesis testing will be performed.

11.5.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint is:

- The Subject Satisfaction Questionnaire administered at Visit 7 (Week 40/Final Visit).

11.6 Safety Endpoints

Safety endpoints will be reported on the All Treated population. Safety assessments will be summarized in tables using descriptive statistics and in individual by-subject listings. No statistical tests will be performed for any of the safety assessments.

Treatment-emergent AEs (TEAEs) will be defined as events that emerge having been absent prior to enrollment in this study or worsen relative to the pre-enrollment state. Summaries of AEs will be limited to TEAEs. The number and percentage of subjects reporting events under each System Organ Class (SOC) and preferred term (PT) will be summarized. At each level of summarization, a subject will be counted only once if he or she reported one or more events. The severity of TEAEs and relationship to the study drug will be summarized in a similar manner. For summaries of relationship to the 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. All TEAEs continuing, but not worsening, after enrollment in this study will also be tabulated.

Treatment-emergent AEs, vital signs, and clinical laboratory measurements will be summarized using descriptive statistics. For vital signs, change from Baseline values will also be summarized. For all safety variables, subject data listings will be provided.

Local signs and symptom assessments will include active assessments of erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation using the scales described under Section 10.5.1.

11.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) terminology will be used to classify all AEs with respect to SOC and PT.

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

11.6.2 Vital Signs and Physical Examinations

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

11.6.3 Clinical Laboratory Results

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. Baseline is defined as the last non-missing value prior to enrollment in this study.

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

11.7 Interim Analysis

No interim analysis is planned.

12 STUDY MANAGEMENT

12.1 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 institutional review board (IRB) to have direct access to all documents pertaining to the study. The Investigator is to notify the Sponsor immediately 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 Good Clinical Practice (GCP)-ICH, and their agreement with the source data. The monitor will also verify the correct use of the study drug. At 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 clinical research associate, as needed, regarding study concerns and/or questions. Contact information is provided in the Study Reference Manual for the site.

12.2 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.

12.3 Protocol Deviations

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

12.4 Withdrawal of Subjects

Subjects or Investigators may choose to discontinue a subject's participation in the study at any time. Subjects may be withdrawn from the study because of any 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 10.6.4.
- **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 the subject is stable to the satisfaction of the Investigator in consultation with the medical monitor.
- **Lost to Follow-up:** Confirmed at minimum by two phone calls and a traceable letter without answer.
- **Subject Request:** Subject requests, for any reason (eg, AE), to be withdrawn or withdraws his or her consent.
- **Protocol Deviation:** 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, subject's relocation, etc. If a subject becomes pregnant during the study, she will be withdrawn from the study and followed through conclusion of the pregnancy (Section 10.6.4.1).

If a subject is withdrawn from the study following the start of study drug, all Visit 7 (Week 40/Final Visit) assessments should be completed. Subjects withdrawn from the study will not be replaced.

12.5 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.

12.6 Publication Policy

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

13 ETHICS

13.1 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.

13.2 Institutional Review Boards

This protocol (and any changes), all consent 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 physician-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 take place followed by IRB approval. Review and approval by the IRB for continuation of the study must take place at least once a year.

13.3 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 or 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 or she is willing to sign a statement of informed consent. Only subjects who voluntarily sign the ICF may enter the study.

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

The original signed ICF will remain in the Investigator's files. The Investigator or designee will indicate in each subject's source documents that he or she has informed the subject about the study and its procedures, the subject has signed and dated the ICF, 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 subject's willingness to continue in the study.

13.4 Subject Confidentiality

The Sponsor will ensure 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.

The investigative site assigns a unique subject identification code 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.

13.5 Records Retention

The Investigator must maintain essential study documents (protocol and amendments, source documentation corresponding to all information contained in the CRFs, signed ICF 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.

13.6 Financing

Funding for this study will be agreed upon 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 1 year after the completion of the study.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and the Investigator will take 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 Department may conduct periodic audits of the study processes, including, but not limited to, auditing the clinical site, laboratories, vendors and contract research organizations CROs, the clinical database, and the final study report.

15 DATA HANDLING AND RECORD KEEPING

This study will use web-based, 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 eCRFs 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 username and password. Only the person who owns the username and password will enter the system using that username 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 remote data capture (RDC) system 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 and approval 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.

16 REFERENCE LIST

Not applicable.

APPENDIX 1: Subject Satisfaction Questionnaire

The following 8 questions will be asked of the subject at Visit 7 (Week 40/Final Visit):

1. How satisfied are you with how easy this product is to use?
2. How satisfied are you with how this product feels on your skin after treatment?
3. How satisfied are you with the odor of this product after treatment?
4. How satisfied are you with the color of this product after treatment?
5. How satisfied are you with the ease of application of the product to your skin?
6. How satisfied are you with the ease in which this product fits into your daily routine?
7. How satisfied are you with this product compared to other products you have previously used for rosacea, such as gels and creams?
8. Overall, how likely are you to use this product with other rosacea treatments?
9. Overall, how likely are you to recommend this product to a friend?
10. Overall, how satisfied are you with this product?

Answers to Questions 1 through 9 will be selected from the following:

- 1 = Very Satisfied
- 2 = Satisfied
- 3 = Somewhat Satisfied
- 4 = Dissatisfied
- 5 = Very Dissatisfied

The answer to Questions 10 and 11 will be selected from the following:

- 1 = Very Likely
- 2 = Likely
- 3 = Somewhat Likely
- 4 = Unlikely
- 5 = Very Unlikely

APPENDIX 2: Acknowledgment Of Receipt And Review Of Protocol

Protocol Number: FX2016-13, Version 1

Protocol Title: An Open-Label Study to Evaluate the Long-Term Safety of Topical Administration of FMX103 for 40 weeks in the Treatment of Moderate to Severe Facial Papulopustular Rosacea (Study FX2016-13)

I hereby acknowledge receipt and review of the following Protocol:

1. Version 1, dated March 6th, 2017

_____

Principal Investigator Name (Print)

_____ _____

Principal Investigator Signature | Date of Signature (DD MMM YYYY)