

**A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to
Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam
Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea
(FX2016-12)**

ClinicalTrials.gov Identifier: NCT04608500

Final Protocol, Version 3.0 (Amendment 2), dated 12-May-2017

Final Protocol, Version 2.0 (Amendment 1), dated 06-Mar-2017

Final Protocol, Version 1.0, dated 20-Jan-2017

CLINICAL PROTOCOL

Title Page

Study Title: A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (FX2016-12)


Sponsor: Foamix Pharmaceuticals, Inc.
520 US Highway 22, Suite 305
Bridgewater, NJ 08807

Protocol Identification: FX2016-12

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: 12 May 2017

Version of Protocol: Version 3 (Amendment 2)

Supersedes: Version 2, issued 06 Mar 2017

Prepared by: The Write Company, LLC

Confidentiality Statement

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Signature Page

Title: A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (Study FX2016-12)

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:	A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (Study FX2016-12)	
Protocol No:	FX2016-12	
Study Centers:	Multicenter (approximately 40 sites in the USA)	
Publication (reference):	None	
Phase of Development:	3	
Objectives:	Primary Objectives: <ul style="list-style-type: none">To determine the efficacy of FMX103 1.5% minocycline foam applied topically once daily for 12 weeks in the treatment of rosacea.To evaluate the safety of topical minocycline foam applied once daily for 12 weeks.	
Study Design and Methods:	<p>This is a randomized, multicenter, double-blind, vehicle-controlled, 2-arm study to evaluate the safety and efficacy of FMX103 topical foam containing 1.5% minocycline compared to vehicle, in the treatment of subjects with moderate-to-severe facial papulopustular rosacea. Qualified subjects will be randomized in a 2:1 ratio (active:vehicle) to receive 1 of the following 2 treatments:</p> <ul style="list-style-type: none">FMX103 minocycline foam 1.5%Vehicle foam <p>Subjects will be assigned to 1 of 2 treatments according to the randomization schedule, stratified by investigational site. Subjects will apply (or have applied) the study drug topically once daily for 12 weeks as directed. Subjects will be advised to use the study drug at approximately the same time each day. Both the Investigator and subject will be blinded to the study drug identity.</p> <p>Subjects will return for visits at Weeks 2, 4, 8, and 12. Efficacy evaluations (inflammatory lesion counts and Investigator’s Global Assessment [IGA] score) will be performed at Weeks 4, 8, and 12</p>	

	during the study.																		
Number of Subjects (planned):	The planned enrollment is approximately 750 male and female subjects. Subjects will be randomly assigned to the two treatment groups, FMX103 1.5% and vehicle, in a 2:1 ratio, respectively.																		
Diagnosis and Main Criteria for Inclusion:	<p>Healthy male or non-pregnant females, aged ≥18 years with a clinical diagnosis of moderate to severe facial papulopustular rosacea, defined as the presence of:</p> <ul style="list-style-type: none">At least 15 and not more than 75 inflammatory facial lesions (ie, papules/pustules), andAn IGA of rosacea severity of moderate or severe using the following scale: <table><tr><th>Score</th><th>Grade</th><th>Description</th></tr><tr><td>0</td><td>Clear</td><td>No inflammatory papules or pustules</td></tr><tr><td>1</td><td>Almost clear</td><td>Few inflammatory papules or pustules</td></tr><tr><td>2</td><td>Mild</td><td>Several inflammatory papules or pustules</td></tr><tr><td>3</td><td>Moderate</td><td>Moderate number of inflammatory papules or pustules and no nodules</td></tr><tr><td>4</td><td>Severe</td><td>Many inflammatory papules or pustules, and up to 2 nodules</td></tr></table> <ul style="list-style-type: none">Current or history of erythema and/or flushing <p>Subjects must be willing to minimize external factors that might trigger rosacea flare-ups (eg, spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, and alcoholic beverages).</p>	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
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																	
Test Product, Dose and Mode of Administration:	FMX103 minocycline foam 1.5%. Topical application, once daily to the face, for 12 weeks.																		
Reference Therapy:	Vehicle foam. Topical application, once daily to the face, for 12 weeks.																		
Study Duration:	Subject participation in the study will be up to 18 weeks: up to 6 weeks for Screening and Day 0/Baseline, and 12 weeks of study treatment. A safety follow-up telephone call will be conducted 4 weeks after completion of study treatment for <u>only</u> those subjects that do not participate in study FX2016-13 (Open label study) and who presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit).																		
Endpoints and Outcomes:	<p>Efficacy Evaluations</p> <p>The co-primary efficacy parameters, include inflammatory lesion counts and IGA, will be evaluated at Day 0/Baseline and at Weeks 4, 8, and 12 (Final Visit). The Subject Global Assessment will be performed at Weeks 2, 4, 8, and 12 (Final Visit). The subject satisfaction questionnaire will be assessed at Week 12 (Final Visit) only.</p> <p>Safety Evaluations</p> <p>The safety assessments will include adverse events (volunteered, observed, and elicited by general questioning in a non-suggestive manner), physical examinations, vital signs, clinical laboratory tests,</p>																		

	and local signs and symptoms assessments (including erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation) scores.
Statistical Methods:	<p>The primary population for efficacy analysis will be the intent-to-treat (ITT) population, using multiple imputations to impute missing values. Supportive efficacy analyses will be conducted on the per-protocol (PP) population, with no imputation for missing values.</p> <p>The co-primary efficacy endpoints will be the dichotomized IGA score where treatment success is defined as at least a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Week 12 compared to Day 0/Baseline and the absolute change in inflammatory lesion count at Week 12 compared to Day 0/Baseline.</p> <p>The key secondary endpoints will be analyzed hierarchically:</p> <ul style="list-style-type: none"> • Dichotomized IGA score where treatment success is defined as a 2-step improvement in score at Week 12 compared to Day 0/Baseline. • Percent change in inflammatory lesion count at Week 12 compared to Day 0/Baseline. <p>Continuous efficacy endpoints will be analyzed using analysis of covariance (ANCOVA). Dichotomized efficacy endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test.</p> <p>The tolerability and safety of topical minocycline foam applied daily for 12 weeks will be evaluated using summary statistics and individual subject data listings.</p> <p>The active treatment group will be tested against vehicle at the 0.05 two-sided level of significance. No statistical tests will be performed for any of the safety assessments.</p>

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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
BOCF	Baseline observation carried forward
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRO	Contract Research Organization
eCRF	Electronic case report form
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 System
ITT	Intent-to-treat (population)
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model for repeated measures
OC	Observed cases
OTC	Over-the-counter
PP	Per-protocol (population)
PT	Preferred term
RBC	Red blood cell
RDC	Remote data capture
SAE	Serious adverse event
SAP	Statistical Analysis Plan
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	Foamix Pharmaceuticals, Inc. 520 US Highway 22 Bridgewater, NJ 08807	Sponsor

External – Contract Research Organization (CRO)

Name	Affiliation / Address / Telephone Number	Responsibility
PPD	PPD	PPD

3 INTRODUCTION

Papulopustular rosacea is a chronic disorder affecting both the skin and the eye. 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.

Foamix has developed a topical minocycline foam product that is being evaluated for safety and efficacy in the treatment of rosacea. Minocycline hydrochloride is an established broad spectrum antibiotic that is used orally in the treatment of 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 has been evaluated in a Phase 2 study at two minocycline concentrations, 1.5% and 3%. The study included 232 subjects (males/females, aged ≥ 18 years) with moderate-to-severe papulopustular rosacea defined by the Investigator's Global Assessment (IGA) score and with ≥ 12 inflammatory facial lesions (papules/pustules) at Day 0/Baseline. Subjects were treated with FMX103 1.5%, FMX103 3%, or vehicle foam, once daily for 12 weeks. Efficacy and safety were evaluated at Weeks 2, 4, 8, and 12, with an additional safety follow-up visit at Week 16. The primary efficacy end point was the absolute change in inflammatory lesion count at Week 12. Other assessments included IGA improvement of ≥ 2 grades and reaching an IGA score of "clear" or "almost clear" (IGA 0/1), clinical assessment of erythema, and safety and tolerability.

At Week 12, both the 1.5% and 3% doses of FMX103 significantly reduced the number of papules and pustules vs. vehicle (both $p < 0.001$, intent-to-treat [ITT] population). The mean reduction in lesion count from Day 0/Baseline was 21.1 for the FMX103 1.5% dose, 19.9 for the FMX103 3% dose, and 7.8 for the vehicle. The corresponding percent reductions were 61.4% and 55.5% for the 1.5% and 3% doses, respectively, and 29.7% for the vehicle.

Both the 1.5% and 3% doses of FMX103 were statistically significantly better than vehicle in improving IGA scores by ≥ 2 grades at week 12 ($p = 0.002$ and $p = 0.032$, respectively). Both doses were also statistically significantly better than vehicle in achieving an IGA of "clear or almost clear" (score 0/1) at Week 12 ($p = 0.001$ and $p = 0.041$, respectively). Both FMX103 1.5% and 3% doses appeared to be generally safe and well-tolerated. Treatment-related dermal reactions were reported in 1 subject from the FMX103 1.5% dose group (considered mild) and in a few subjects

from the FMX103 3% dose group (mild, n=1; moderate, n=2; severe, n=1). No treatment-related systemic adverse events (AEs) were reported and discontinuation due to AEs (eczema, n=1; rosacea, n=1; burning sensation, n=1) was reported in 3 subjects in the FMX103 3% dose group.

As a consequence of the above, the FMX103 1.5% dose concentration has been selected for further development. This Phase 3 study will further assess the safety and efficacy of topical minocycline HCl foam, 1.5%, applied once daily compared with vehicle foam for the treatment of moderate-to-severe papulopustular rosacea.

4 STUDY OBJECTIVES

The primary objectives of the study are:

- To determine the efficacy of FMX103 1.5% minocycline foam applied topically once daily for 12 weeks in the treatment of rosacea.
- To evaluate the tolerability and safety of topical minocycline foam applied once daily for 12 weeks.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is a randomized, multicenter, double-blind, vehicle-controlled, 2-arm study to evaluate the safety and efficacy of FMX103 topical foam containing 1.5% minocycline compared to vehicle, in the treatment of subjects with moderate-to-severe facial papulopustular acne rosacea.

Qualified subjects will be randomized in a 2:1 ratio (active:vehicle) to use once daily one of the following two treatments:

- FMX103 minocycline foam 1.5%
- Vehicle foam

Subjects will be assigned to 1 of 2 treatments according to the randomization schedule, stratified by investigational site. Subjects will apply (or have applied) the study drug topically once daily for 12 weeks as directed. Subjects will be advised to use the study drug at approximately the same time each day about 1 hour before bedtime. Both the Investigator and subject will be blinded to the study drug identity.

Subjects will return for visits at Weeks 2, 4, 8, and 12. Efficacy evaluations (inflammatory lesion counts [\[Section 9.1.1\]](#) and IGA score [\[Section 9.1.2\]](#)) will be performed at Weeks 4, 8, and 12 during the study. Other assessments will be performed as described in [Section 9](#) and [Section 10](#).

5.2 Rationale for Study Design and Dose Selection

A randomized, multicenter, double-blind, vehicle-controlled study design has been selected in order to assess the efficacy of the study drug. The subjects will be selected according to predefined entry criteria. The study treatment duration of 12 weeks is expected to be sufficient to show a treatment effect.

The concentration of minocycline in the composition was selected according to formulation integrity and stability considerations and based on the results of Phase 2 Study FX2015-10 (described above in [Section 3](#)).

Because of the mode of action of tetracycline drugs, the primary efficacy endpoints will be the effect on inflammatory lesion counts and IGA scores ([Section 9](#)).

6 STUDY POPULATION

The study will randomize approximately 750 subjects to active or vehicle treatment (in a 2:1 ratio) at approximately 40 sites in the US.

6.1 Inclusion Criteria

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

1. Male or female ≥ 18 years-of-age.
2. Moderate-to-severe rosacea (as per the IGA score; [Table 3](#)) on the proposed facial treatment area consisting of:
 - a. At least 15 and not more than 75 facial papules and pustules, excluding lesions involving the eyes and scalp;
 - b. No more than 2 nodules on the face.
3. Presence of or history of erythema and/or flushing on the face.
4. If a female 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.
5. Willing to minimize external factors that might trigger rosacea flare-ups (eg, spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, and alcoholic beverages).
6. Subjects who use make-up must have used the same brands/types of make-up for a minimum period of 14 days prior to study entry and must agree to use the same make-up, brand/type, or frequency of use, throughout the study.
7. Completed and signed an appropriately administered Informed Consent Form (ICF) prior to any study-related procedures.

6.2 Exclusion Criteria

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

1. Woman who is pregnant, lactating, or planning to become pregnant during the study period.
2. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea.

3. Moderate or severe rhinophyma, dense telangiectasia (score 3, severe; [Section 10.7.2.2](#)), or plaque-like facial edema.
4. Excessive facial hair (eg, beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.
5. History of hypersensitivity or allergy to minocycline, any other tetracycline, or of any other component of the formulation.
6. Severe erythema, dryness, scaling, pruritus, stinging/burning, or edema.
7. Active ocular rosacea (eg, conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics.
8. Use within 6 months prior to Day 0/Baseline of oral retinoids (eg, Accutane[®]) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
9. Initiation of use of estrogens or oral contraceptives less than 3 months prior to Day 0/Baseline.
10. Use within 1 month prior to Day 0/Baseline of:
 - a. Topical retinoids to the face.
 - b. Systemic antibiotics known to have an impact on the severity of facial rosacea (eg, containing tetracycline and its derivatives, erythromycin and its derivatives, sulfamethoxazole, or trimethoprim). Subjects requiring systemic antibiotics not known to affect rosacea will be considered on a case-by-case basis.
 - c. Systemic corticosteroids (Note: intranasal and inhalational corticosteroids do not require a washout and maybe used throughout the trial if the subject is on a stable dose).
11. Use within 2 weeks prior to Day 0/Baseline of:
 - a. Topical corticosteroids.
 - b. Topical antibiotics.
 - c. Topical medications for rosacea (eg, metronidazole).
12. Use of a sauna during the 2 weeks prior to Day 0/Baseline and during the study.
13. Had wax epilation of the face within 2 weeks prior to Day 0/Baseline.
14. Active bacterial folliculitis.
15. Consumption of excessive alcohol, abuse of licit or illicit drugs, or a condition that, in the opinion of the Investigator, could compromise the subject's ability to comply with study requirements.
16. Participation in activities that involve excessive or prolonged exposure to sunlight or weather extremes, such as wind or cold.

17. Presence of any clinically significant condition or situation, other than the condition being studied, that in the opinion of the Investigator would interfere with the study evaluations or optimal participation in the study.
18. Participation in an investigational drug study (ie, subject has been treated with an investigational drug) within 30 days prior to Day 0/Baseline. Subjects who are participating in non-treatment studies such as observational studies or registry studies can be considered for inclusion.
19. Previously enrolled in this study.
20. Prior laser therapy (for telangiectasia or other conditions), electrodesiccation, or phototherapy (eg, ClearLight[®]) to the facial area within 180 days prior to Day 0/Baseline.
21. Prior cosmetic procedures (eg, facials) that may affect the efficacy and safety profile of the investigational product within 14 days prior to Day 0/Baseline.

7 STUDY PROCEDURES

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

The eligible subject who is willing to participate in the study will then sign an appropriately administered ICF prior to any study-related procedures being performed.

Procedures at the Screening Visit will include obtaining blood and urine samples for clinical laboratory tests. The results of these tests must be no more than 45 days old at the time of the Day 0/Baseline Visit and randomization.

If a subject who has agreed to participate in the study, has signed the ICF and is currently undergoing rosacea therapy identified in Exclusion Criteria [10](#) and [11](#), they must first enter a washout period (ie, 1 month or 2 weeks, as specified in Exclusion Criteria [10](#) and [11](#), respectively) during the screening period. Screening procedures are to be performed as defined in the Screening Visit ([Section 7.1](#)).

The schedule of study assessments and procedures and the time point at which they will be performed during the study is presented in [Table 1](#). If a subject prematurely withdraws from the study, the subject should return to the study site for an early termination visit during which all evaluations described under Final Visit 5/Week 12 must be performed.

Table 1 Schedule of Study Assessments and Procedures – Study FX2016-12

Assessment or Procedure	Screening	Day 0 / Baseline ⁰	Visits/Early Follow-up				Final Visit ^b	Safety Follow-up ^f
			EF	2	3	4		
Visit		1	1	2	4	8	12	
Informed consent	X							
Demographic data	X							
Assign subject identification	X							
Medical/surgical/medication history	X							
Inclusion/exclusion criteria	X	X						
Physical examination, height, weight ^c		X					X	
Blood pressure/heart rate ^d		X		X	X	X	X	
Blood and urine samples for clinical laboratory tests	X						X	
Urine pregnancy test (females of childbearing potential only)	X	X			X	X	X	
Lesion counts	X	X			X	X	X	
Investigator's Global Assessment	X	X			X	X	X	
Subject Global Assessment				X	X	X	X	
Subject Satisfaction Questionnaire							X	
Local signs and symptoms assessments ^e	X	X		X	X	X	X	
Photography [†]		X			X	X	X	
Randomization		X						
Concomitant medications		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Perform drug accountability				X	X	X	X	
Collect used drug canister(s)				X	X	X	X	
Dispense study drug		X			X	X		
Schedule/confirm next visit	X	X	X	X	X	X		

EF – Early Follow-up telephone call, no visit; † only for study centers participating in subject photography (Section 9.3)

- Day 0/Baseline must occur within 45 days of Screening. Blood test results must not show clinically significant abnormalities.
- If a subject prematurely withdraws from the study, all evaluations described under Visit 5/Week 12 (Final Visit) must be performed at an Early Termination Visit.
- Height to be measured only at Day 0/Baseline.
- Measure blood pressure and heart rate after the subject has been sitting for at least 5 minutes at rest.
- 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.
- A safety follow-up telephone call will be made 4 weeks after Visit 5/Week 12 (Final Visit) for only those subjects that do not participate in study FX2016-13 (Open label study) and presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit).

7.1 Screening Visit

- Obtain a signed and dated, written ICF prior to any study-related procedures.
- Obtain demographic data.
- Using the Interactive Response Technology System (IRT), assign the subject an identification number.
- Obtain medical/surgical history ([Section 10.1](#)).
- Obtain history of prior medication usage (including previous use of rosacea medications); record start and stop dates of any medications used in the last 3 months ([Section 10.2](#)).
- Assess eligibility according to the inclusion ([Section 6.1](#)) and exclusion criteria ([Section 6.2](#)).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test ([Section 10.6.1](#)).
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory ([Section 10.6.2](#)).
- Perform facial lesion count of inflammatory lesions ([Section 9.1.1](#)).
- Perform IGA ([Section 9.1.2](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Schedule/confirm the next study visit.

7.2 Visit 1, Day 0/Baseline Visit

- Confirm eligibility according to the inclusion ([Section 6.1](#)) and exclusion criteria ([Section 6.2](#)).
- Perform physical examination including height and weight ([Section 10.5](#)).
- Measure blood pressure and heart rate ([Section 10.4](#)).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test ([Section 10.6.1](#)).
- Perform facial lesion count of inflammatory lesions ([Section 9.1.1](#)).
- Perform IGA ([Section 9.1.2](#)).
- Perform photography ([Section 9.3](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Randomize the subject using the IRT when all criteria have been met.
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).

- Dispense one kit (2 canisters) of study drug.
- Dispense facial cleanser and moisturizer.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.3 Early Follow-up, Week 1 (±3 Days)

An early follow-up telephone call will be made 1 week after Visit 1, Day 0/Baseline.

- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Confirm that subject continues to use only the provided facial cleanser and moisturizer.
- Review application instructions to confirm that the subject continues to use the study drug as directed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.4 Visit 2, Week 2 (±3 Days)

- Measure blood pressure and heart rate ([Section 10.4](#)).
- Have the subject complete the Subject Global Assessment ([Section 9.2.3](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Confirm that subject continues to use only the provided facial cleanser and moisturizer.
- Review application instructions to confirm that the subject continues to use the study drug as directed.
- Perform drug accountability to assess compliance ([Section 8.2](#)).
- Collect used study canister (if applicable).
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.5 Visit 3, Week 4 (±3 Days)

- Measure blood pressure and heart rate ([Section 10.4](#)).
- 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 9.2.3).
- Perform photography (Section 9.3).
- Perform local signs and symptoms assessments (Section 10.7.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test (Section 10.6.1).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.8).
- Perform drug accountability to assess compliance (Section 8.2).
- Collect used study drug canister (if applicable).
- Dispense one kit (2 canisters) of study drug.
- Confirm that subject continues to use only the provided facial cleanser and moisturizer and dispense additional quantities as required.
- Review application instructions to confirm that the subject continues to use the study drug as directed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.6 Visit 4, Week 8 (±3 Days)

- Measure blood pressure and heart rate (Section 10.4).
- 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 9.2.3).
- Perform photography (Section 9.3).
- Perform local signs and symptoms assessments (Section 10.7.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test (Section 10.6.1).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.8).
- Perform drug accountability to assess compliance (Section 8.2).
- Collect used study drug canister (if applicable).
- Dispense one kit (2 canisters) of study drug.

- Confirm that subject continues to use only the provided facial cleanser and moisturizer and dispense additional quantities as required.
- Review application instructions to confirm that the subject continues to use the study drug as directed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.7 Visit 5, Week 12 (-3/+5 days) / Final Visit or Early Termination

- Perform physical examination including weight (Section 10.5).
- Measure blood pressure and heart rate (Section 10.4).
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory (Section 10.6.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test (Section 10.6.1).
- Perform facial lesion count of inflammatory lesions (Section 9.1.1).
- Perform IGA (Section 9.1.2).
- Perform photography (Section 9.3).
- Perform local signs and symptoms assessments (Section 10.7.2).
- Have the subject complete the Subject Global Assessment (Section 9.2.3).
- Have the subject complete the Subject Satisfaction Questionnaire (Section 9.2.4).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.8).
- Collect all used and full study drug canisters.
- Perform drug accountability to assess compliance and record the date of the last dose (Section 8.2).
- Schedule/confirm a safety follow-up telephone call 4 weeks from Visit 5/Week 12 (Final Visit) date (± 5 days) only for subjects that will not participate in study FX2016-13 (Open label study) (Section 7.9) and presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit).

7.8 Safety Follow-Up (± 5 days)

A safety follow-up telephone call will be made 4 weeks after Visit 5/Week 12 (Final Visit) for only those subjects that do not participate in study FX2016-13 (Open label study) and presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit). Follow up on these adverse events and any new concomitant medications will be recorded.

8 STUDY TREATMENTS

This study will include FMX103 minocycline foam 1.5% and vehicle foam.

8.1 Treatments Administered

The description of study drug kits and treatments is shown below in [Table 2](#).

Table 2 Study Drug Kits and Treatments – Study FX2016-12

Dosage form description:	Foam containing minocycline HCl 1.5% or vehicle foam
Package description:	Canisters, each containing 35 g of the clinical trial supply foam
Daily dose:	Once daily application of a sufficient amount of foam to cover the entire face. Estimated maximum is 0.5 g of drug product containing 7.5 mg (1.5% active) or 0.0 mg (vehicle) of minocycline.
Cumulative maximal dose for dosing (12 weeks):	630 mg (1.5%) minocycline
Dispensing:	Kits consisting of 2 canisters, each canister containing 35 g of FMX103 minocycline formulation, 1.5%, or vehicle dispensed at Visit 1 (Day 0/Baseline), Visit 3 (Week 4), and Visit 4 (Week 8).

8.1.1 Dosing Instructions

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

Study drug kits containing 2 canisters of investigational drug will be dispensed at Visit 1 (Day 0/Baseline), Visit 3 (Week 4), and Visit 4 (Week 8).

After shaking the canister well, a small amount of study drug (about ½ gram or a cherry-sized amount) should be expressed from the canister onto the finger tips and then applied as a thin layer over all areas of the face. Additional drug may be used as needed to ensure the entire face is treated.

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

8.1.2 Manufacturer

The manufacturer of the investigational product is ASM Aerosol-Service AG, Moehlin, Switzerland.

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% and vehicle canisters must be stored at 2°C – 8°C until being dispensed to the subject. Subsequently, they must be stored at 20°C – 25°C (refer to USP Controlled Room Temperature). 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 use of the study drug. The Investigator or designee will verify the contents of the drug shipment and confirm receipt of the study drug in the 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 bottles of study drug will be returned to the Sponsor or designee by the time of the site's close-out visit. Receipt, distribution, and return of the study drug must be properly documented on forms provided by the Sponsor or designee.

8.4 Method of Assignment of Study Drug

After pretreatment, clinical evaluations and all other Screening procedures have been completed, authorized site personnel will acknowledge that the applicable subject met all the specified inclusion criteria ([Section 6.1](#)) and none of the exclusion criteria ([Section 6.2](#)). Assignment to a treatment group will then follow a predetermined list of randomization numbers, with each successive number receiving 1 of the 2 treatments in random order. Authorized site personnel will use the IRT system to assign a kit number that corresponds to the randomization schedule. The kit box with the assigned kit number will be dispensed to the subject.

The randomization code will be provided by Premier Research, Research Triangle Park, NC.

8.5 Selection and Timing of Doses in the Study

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

8.6 Blinding

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

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

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

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

If unblinding is necessary, the subject will be withdrawn from the study and Early Termination Visit (ie, Visit 5 [Week 12]) assessments will be completed.

8.7 Prior/Concomitant Therapy

As necessary, subjects should use the facial cleanser *Cetaphil Gentle Skin Cleanser* and the facial moisturizer *Eucerin Daily Protection Broad Spectrum SPF30 Face Lotion*. Both products will be provided by the Sponsor. Alternative, non-medicated cleansers or moisturizers may be used if agreed to by the Sponsor.

The use of or change in the dose of any and all 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. Therapies (medication and non-medication therapies) not restricted by the protocol may be used. Non-prohibited chronic therapies being used at Day 0/Baseline may be continued. If a female subject is using an oral contraceptive product, she should have been on the same product for at least 3 months and she should continue using the same or equivalent product for the duration of the study.

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

All topical or systemic medications listed in the exclusion criteria are prohibited during this study. Similarly, no other topical medications are permitted to be used on the face during this period.

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 is not postmenopausal (defined as amenorrhea >12 consecutive months). Females of childbearing potential must have a negative urine pregnancy test and, if they are sexually active or become sexually active during the study, must use an effective method of birth control such as those listed below during the course of the study. The following is not an all-inclusive list; the subject must discuss with the Investigator the most appropriate form of birth control:

- Hormonal methods
 - Oral contraceptives – (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 kits (empty/used/unused) at the appropriate visits. The study site personnel will question the subject on the history of study drug use since the last visit. A subject who deviates significantly from the prescribed dosage will be counseled.

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 Co-Primary Efficacy Assessments

The co-primary efficacy assessments will include the inflammatory lesion counts and the IGA of severity of disease. Lesion counts, IGA, and other efficacy evaluations 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 will be performed at Screening and Visit 1 (Day 0/Baseline) to confirm eligibility, and again at Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/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 will be performed at Screening and Visit 1 (Day 0/Baseline) to confirm eligibility, and again at Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/Final Visit).

Table 3 IGA Scale for Rosacea – Study FX2016-12

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 [REDACTED] CCI Efficacy Assessments

9.2.1 Percent Change in Inflammatory Lesion Counts

The percent change in inflammatory lesion counts at Visit 5 (Week 12/Final Visit) compared to Visit 1 (Day 0/Baseline) will be evaluated.

9.2.2 Interim Change in Inflammatory Lesion Counts

The absolute [REDACTED] CCI change in inflammatory lesion counts at Visit 3 (Week 4) and Visit 4 (Week 8) compared to Visit 1 (Day 0/Baseline) will be evaluated.

9.2.3 Subject Global Assessment

This score will be obtained from the subject at Visit 2 (Week 2), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/Final Visit) using the questionnaire in [Appendix 1](#).

9.2.4 Subject Satisfaction Questionnaire

A subject satisfaction questionnaire ([Appendix 2](#)) will be administered at Visit 5 (Week 12/Final Visit).

9.3 Photography

Photography will be performed at selected study centers only. Study centers should refer to their specific Clinical Trial Agreement to confirm participation.

Photography of the full face will be performed at Day 0/Baseline and at Weeks 4, 8, and 12 using recognized methods. The equipment and techniques for this photography and for archiving the images are described in the Study Manual. Photographs will be reviewed at the site and by the sponsor for quality. Photographs will not be used to assess the lesion counts or the IGA, but will be archived to be available for subsequent review, if required, by the sponsor, auditors, or the FDA.

10 SAFETY ASSESSMENTS

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

10.1 Medical/Surgical History

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

10.2 Medication History

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

10.3 Concomitant Medications

All topical or systemic medications listed in the exclusion criteria are prohibited. No other topical medications are permitted to be used on the face. All medication that the subject is currently taking or any change in medication or dosage since the last visit will be documented throughout the study. The use of or change in the dose of any and all concomitant medication, either prescription or 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.

10.4 Vital Signs

Heart rate and blood pressure (BP) will be measured at all post-Day 0/Baseline 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.

10.5 Physical Examination

A complete physical examination (excluding the genitourinary examination) will be performed.

Weight will be recorded at the Visit 1 (Day 0/Baseline) and Visit 5 (Week 12/Final Visit). Height will be measured at Visit 1 (Day 0/Baseline) only.

10.6 Clinical Laboratory Tests

Serum chemistry, hematology and urinalysis will be evaluated at the Screening Visit and Visit 5 (Week 12/Final Visit). All clinical laboratory tests will be performed at 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 FX2016-12

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

10.6.1 Urine Pregnancy Test

A urine pregnancy test will be performed on all females of childbearing potential at the Screening Visit, Visit 1 (Day 0/Baseline), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/Final Visit) or when a subject prematurely withdraws from the study.

10.6.2 Sample Collection, Storage, and Shipping

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

10.7 Other Safety Measurements

10.7.1 Local Signs and Symptoms Assessments

The severity of each of the following local signs and symptoms will be measured at Screening, Visit 1 (Day 0/Baseline), and at each study visit: 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 adverse events, unless a sign/symptom is believed to have been related to the study medication or is the reason for discontinuation from the study.

10.7.1.1 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

10.7.1.2 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

10.7.1.3 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

10.7.1.4 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

10.7.1.5 Dryness/Xerosis

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

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

10.7.1.6 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

10.7.1.7 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

10.7.1.8 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

10.8 Adverse Events

10.8.1 Method of Determining Adverse Events

Safety assessments will include recording adverse events reported spontaneously by the subject or observed by the Investigator. AEs will be recorded at each visit on the appropriate CRF. Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded 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 10.8.4](#)) and recorded in the subject's source documents, and the results will be provided to the Sponsor.

For AE definitions and reporting requirements, refer to [Section 10.8.2](#) and [Section 10.8.3](#), respectively.

10.8.2 Adverse Event Definitions

10.8.2.1 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.

10.8.2.2 Serious Adverse Events

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

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

10.8.2.3 Severity of Adverse Events

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

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

10.8.2.4 Relationship of Adverse Events to Study Treatments

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

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

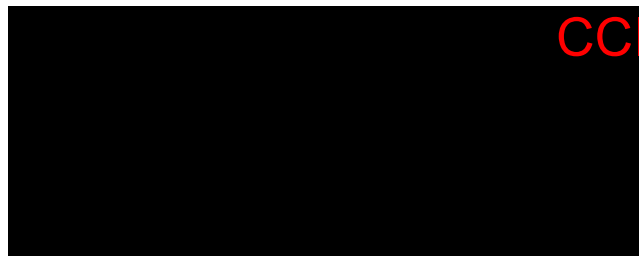
10.8.2.5 Adverse Events Expectedness

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.

10.8.3 Reporting Adverse Events

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

Any SAEs occurring in a subject receiving study drug must be reported to the Sponsor or designee within 24 hours of the site being informed of the event, even if the event does not appear to be drug-related. The report must be done by faxing the completed SAE Report Form to the Sponsor or designee. Any pertinent follow-up information should be provided in a similar manner. Contact information is provided below:



10.8.4 Adverse Event Follow-up

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

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

10.8.4.1 Pregnancy Reporting

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

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

A urine pregnancy test will be performed on all females of childbearing potential as described in [Section 10.6.1](#).

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, missed or late menstrual period). If a subject or Investigator suspects that the subject may be pregnant at any time before or during the study, the study drug must be withheld until the results of laboratory pregnancy testing are available. The Sponsor and site monitor must be notified and 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.

10.8.5 Clinically Significantly Abnormal Laboratory Results

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

10.9 Appropriateness of Safety Measurement

The safety assessments to be utilized 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 (SAP) will be finalized prior to breaking of the study blind.

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

11.2 Determination of Sample Size

In the Phase 2 Study FX2015-10, the proportion of subjects with an IGA score of 0 or 1 after [REDACTED] of treatment was [REDACTED] in the FMX103 1.5% dose group compared to [REDACTED] for the vehicle dose group. Table 5 provides alternate assumptions on this primary response criterion with corresponding implications on sample size. Power was set to 90% and a type-1 error was set to a two-sided test with a 0.05 level of significance. Sample size was calculated based on Fisher's Exact test.

Table 5 Sample Size Calculations Based on IGA Scores after [REDACTED] of Treatment in Phase 2 Study FX2015-10

Vehicle IGA (Score 0,1)	FMX103 1.5% IGA (Score 0,1)	Sample Size (Vehicle, Active)
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Assuming a [REDACTED] dropout rate, 500 subjects receiving FMX103 and 250 subjects receiving vehicle will provide at least 90% power for a statistically significant difference on an IGA score of 0 or 1.

For the co-primary endpoint of change from Day 0/Baseline to [REDACTED] in inflammatory lesion count, in the Phase 2 study the FMX103 1.5% dose group had a mean reduction of [REDACTED] lesions whereas the vehicle had a mean reduction of [REDACTED] lesions. The standard deviation was [REDACTED]. For a 90% power, [REDACTED] and [REDACTED] subjects in the FMX103 1.5% and vehicle groups, respectively, will be needed. Therefore, the sample size needed to provide at least 90% power for both co-primary endpoints is [REDACTED] and [REDACTED] subjects in the FMX103 1.5% and vehicle groups, respectively.

11.3 Analysis Populations

The following populations will be defined for analysis:

- Intent-to-Treat (ITT) population: all randomized subjects.
- Per-Protocol (PP) population: defined as the subset of the ITT population without any protocol deviations that may have an impact on the efficacy assessments. Subjects to be included in the PP population will be determined by the Sponsor/CRO prior to the unblinding of the study.

Subjects may be included in the PP population if all of the following are met:

- Have met all inclusion/exclusion criteria
- Have not administered any interfering concomitant medications
- Were not subject to a randomization error
- Completed treatment through Week 12

- Were greater than 80% compliant with study medication where % compliance is defined as:

$$\% \text{ Compliance} = 100 \times (\text{expected treatment duration in days minus \# days a dose was missed}) / (\text{expected treatment duration in days})$$

- **Safety Population:** all randomized subjects who use any study product. Subjects who have no post-Day 0/Baseline assessments will be included in the Safety population unless all dispensed study drug is returned unused.

The ITT population will be the primary population for efficacy analysis. The PP population will be secondary for the co-primary endpoints only. The Safety population will be used for the analyses of safety endpoints.

All efficacy analyses will be conducted according to the randomized treatment assignment; all safety analyses will be conducted according to the treatment actually received.

11.4 Subject Accounting, Demographics, and Day 0/Baseline Characteristics

Demographics, Day 0/Baseline characteristics, and prior and concomitant medications will be summarized by treatment. Study completion status and reasons for discontinuation will also be displayed by treatment.

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

11.5 Efficacy Endpoints

The primary population for all efficacy analyses will be the ITT population. For the analyses of the co-primary and secondary efficacy endpoints based on the ITT population, a variety of methods will be used to impute missing data, including multiple imputation (MI), last-observation-carried forward (LOCF), and Day 0/Baseline observation carried forward (BOCF). MI will be the primary imputation method. Sensitivity analyses using LOCF and BOCF will be performed only on the co-primary efficacy endpoints to assess the robustness of alternate imputation assumptions. For the continuous efficacy measure, a mixed effects model for repeated measures (MMRM) analysis will also be conducted as a sensitivity analysis. All supportive analyses using the PP population will use the Observed-Cases (OC) approach, that is there will be no imputation for missing data at any time point. No other imputations will be made unless otherwise specified.

For all efficacy analyses, subjects will be analyzed according to the treatment group to which they were randomized.

11.5.1 Primary Efficacy Endpoints

The co-primary efficacy endpoints are:

- The absolute change in the inflammatory lesion count at Week 12 compared to Day 0/Baseline.
- The dichotomized IGA score where treatment success is defined as at least a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Week 12 compared to Day 0/Baseline.

The null hypothesis of the equality of the FMX103 1.5% and vehicle means for absolute change from Day 0/Baseline to Week 12 in the inflammatory lesion count and the equality of IGA success rates at Week 12 will each be tested at a two-sided 0.05 level of significance. Change from Day 0/Baseline in inflammatory lesion count will be analyzed using an analysis of covariance (ANCOVA), with treatment as a main effect, Day 0/Baseline inflammatory lesion count as a covariate, and investigational site as a blocking factor. An investigation site-by-treatment interaction term will be included in the ANCOVA model to test for homogeneity among investigational sites.

The dichotomized IGA will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, stratified by investigational site. For dichotomized IGA, the investigational site-by-treatment interaction will be assessed with the Breslow-Day test. Investigational site-by-treatment interaction will be tested at a two-sided 0.1 level, and if significant will be further explored through the examination of descriptive statistics by individual (non-pooled) investigative sites.

For analysis purposes, all investigative sites with fewer than 8 randomized subjects will be combined into a single pooled site. If a resulting pooled site still has fewer than 10 randomized subjects, then this pooled site will be further combined with the smallest unpooled site. This pooling process will continue until there are at least 8 randomized subjects in each pooled site.

11.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The dichotomized IGA score where success is defined as a 2-step improvement in score at Week 12 compared to Day 0/Baseline.
- The percent change in inflammatory lesion count at Week 12 compared to Day 0/Baseline.
- The absolute change from Day 0/Baseline in the inflammatory lesion count and IGA treatment success at the interim visit at Week 8.
- The absolute change from Day 0/Baseline in the inflammatory lesion count and IGA treatment success at the interim visit at Week 4.

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

11.5.3 CCI CCI

- [REDACTED] CCI
- [REDACTED] CCI

11.6 Safety Endpoints

Safety endpoints will be reported on the Safety population. Subjects will be reported according to the treatment they actually received. Safety assessment will be based on descriptive statistics and individual 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 pre-treatment, or worsen relative to the pre-treatment state. Summaries of AEs will be limited to TEAEs. The number and percentage of subjects reporting events under each System Organ Class (SOC) and preferred term (PT) will be summarized for each treatment group. At each level of summarization, a subject will be counted only once if he/she reported one or more events. The severity of TEAEs and relationship to study drug will be summarized in a similar manner. For summaries of relationship to study drug, a subject will be classified according to the closest relationship. For summaries of TEAE severity, a subject will be classified according to the highest severity.

TEAEs, vital signs, and clinical laboratory measurements will be summarized by treatment group using descriptive statistics. For vital signs, change from Day 0/Baseline values will also be summarized. For all safety variables, subject data listings will be provided.

Local signs and symptoms 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 10.7.2](#).

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 prematurely withdraw from the study 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 Day 0/Baseline and at each post-Day 0/Baseline time point. Changes from Day 0/Baseline will also be summarized. Day 0/Baseline is defined as the last non-missing value prior to the first dose of study drug.

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 Day 0/Baseline with the number of subjects with low, normal, or high values at the Final Visit. Day 0/Baseline is defined as the last non-missing value prior to the first dose of study drug.

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

11.7 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 immediately notify the Sponsor of any regulatory authority inspections. The Investigator will be informed about the outcome of any Sponsor audit.

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

Monitoring visits will take place on a regular basis according to the enrollment rate and number of subjects enrolled at each investigational site. During these visits, the monitor will check the completion of the CRF entries, compliance with the study protocol and with GCP-ICH, and their agreement with the source data. The monitor will also verify the correct use of the study drug. At a 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 the IRB's guidelines.

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

12.4 Withdrawal of Subjects

Withdrawn subjects are those who do not complete all evaluations and procedures outlined in the protocol. Subjects who discontinue taking study drug for any reason must also be withdrawn from the study. Subjects may be withdrawn from the study because of 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 10.8.4](#).
- **Abnormal Laboratory Result:** Any clinically significant laboratory abnormality that requires withdrawal of the subject from the study should be considered an AE leading to withdrawal. If possible, laboratory tests will be repeated for any results that were clinically significantly abnormal until the abnormality is resolved or stabilized to the satisfaction of the Investigator in consultation with the medical monitor.
- **Lost to Follow-up:** Confirmed at minimum by two phone calls and a traceable letter without answer.
- **Subject Request:** Subject requests, for any reason (eg, AE), to be withdrawn or withdraws his/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, relocation of subject, etc. If a subject becomes pregnant during the study, the subject will be withdrawn from the study and followed through conclusion of the pregnancy.

If a subject is withdrawn from the study following the start of study drug, all Visit 5 (Week 12/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, which will make reasonable efforts to assure that the results are published in a peer-reviewed journal. As some of the information concerning the investigational product and development activities at the Sponsor may be of a strictly confidential 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 (IRB)

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/her entry into the study (ie, before examinations and procedures associated with selection for the study are initiated). Each subject will have ample opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Following this informative discussion, the subject will be asked if he/she is willing to sign a statement of informed consent. Only subjects who voluntarily sign the ICF may enter the study.

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

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

13.6 Financing

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

Completion of Financial Disclosure Forms will be required before the study starts. Any additions to the primary site personnel will necessitate the completion of new Financial Disclosure Forms. This information will also be collected at site closure and 1 year after the completion of the study.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and 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 (CQA) Department may conduct periodic audits of the study processes, including, but not limited to, auditing the clinical site, laboratories, vendors and CROs, the clinical database, and the final study report.

15 DATA HANDLING AND RECORD KEEPING

This study will use web-based, electronic case report forms (eCRFs) developed through a validated, Electronic Records/Electronic Signatures-compliant platform (US Title 21 CFR Part 11). Foamix Clinical Data Management department or designee will create the 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 FX2016-12.

Section 17.1 describes the changes made to Protocol FX2016-12 Version 1 issued January 20, 2017, via Amendment 1 effective March 6th, 2017.

Section 17.2 describes the changes made to Protocol FX2016-12 Version 2 issued March 6th, 2017, via Amendment 2 effective May 12th, 2017.

17.1 Amendment 1, effective March 6th, 2017

The following is the summary of the changes that were made to Protocol FX2016-12 Version 1 issued January 20, 2017.

Content changes:

New or changed text is **bolded**.

Section(s)	Revision		Rationale
	Old Text	New Text	
Synopsis (Study Centers); Sect. 6 Study Population	...approximately 30 sites...	...approximately 40 sites...	Number of study centers adjusted to account for larger study sample size.
Sect. 11.2 Determination of Sample Size; Table 5 Sample Size Calculations Based on IGA Scores after CCI of Treatment in Phase 2 Study FX2015-10 and text	... CCI CCI ...	Typographic error.
Sect. 11.2 Determination of Sample Size; Table 5 and text	New text inserted in Table 5.	Vehicle IGA (Score 0,1): CCI; FMX103 1.5% IGA (Score 0,1): CCI; Sample Size (Vehicle, Active): CCI	Study sample size calculation based on an assumed CCI reduction in effect difference between active and vehicle, relative to Study FX2015-10 FMX103 1.5% IGA (Score 0,1) v's Vehicle IGA (Score 0,1) observed difference.
As above.	Assuming a CCI dropout rate, CCI subjects receiving FMX103 and CCI subjects...	Assuming a CCI dropout rate, CCI subjects receiving FMX103 and CCI subjects...	Corrected for larger study sample size.
As above.	Therefore, the sample size needed to provide 90% power for both co-primary endpoints is CCI and CCI subjects...	Therefore, the sample size needed to provide at least 90% power for both co-primary endpoints is CCI and CCI subjects...	Corrected for larger study sample size.

Section(s)	Revision		Rationale
	Old Text	New Text	
Synopsis (Statistical Methods); Sect. 11.5.1 Primary Efficacy Endpoints	...treatment success is defined as a 2-step improvement...	...treatment success is defined as at least a 2-step improvement...	Clarification of treatment success criteria.
Synopsis (Number of Subjects (planned); Sect. 6 Study Population	...approximately 450 subjects...	...approximately 600 subjects...	Corrected for larger study sample size.
Sect. 7.2 Visit 1, Day 0/Baseline Visit	New text.	Dispense facial cleanser and moisturizer.	Clarification of the need to dispense cleanser and moisturizer at Day 0/Baseline.
Sect. 7.4	<ul style="list-style-type: none"> Confirm that subject continues to use only the provided facial cleanser. 	<ul style="list-style-type: none"> Confirm that subject continues to use only the provided facial cleanser and moisturizer. 	Reflecting the addition of moisturizer.
Sect. 7.5 and 7.6	<ul style="list-style-type: none"> Confirm that subject continues to use only the provided facial cleanser. 	<ul style="list-style-type: none"> Confirm that subject continues to use only the provided facial cleanser and moisturizer and dispense additional quantities as required. 	Clarification of cleanser and moisturizer re-supply to subjects.
Sect. 8.7 Prior/Concomitant Therapy	<ul style="list-style-type: none"> Subjects should use the facial cleanser <i>Cetaphil Gentle Skin Cleanser</i> (which will be provided by the Sponsor). An alternative, non-medicated cleanser may be used if agreed to by the Sponsor. 	<ul style="list-style-type: none"> As necessary, subjects should use the facial cleanser <i>Cetaphil Gentle Skin Cleanser</i> and the facial moisturizer <i>Eucerin Daily Protection Broad Spectrum SPF30 Face Lotion</i>. Both products will be provided by the Sponsor. Alternative non-medicated cleansers or moisturizers may be used if agreed to by the Sponsor. 	Addition of a SPF-containing moisturizer to support a positive skin care regimen during the study.

Section(s)	Revision		Rationale
	Old Text	New Text	
Synopsis, Endpoints and Outcomes;	The efficacy parameters will include inflammatory lesion counts, IGA at Day 0/Baseline and at Weeks 4, 8, and 12 (Final Visit), and the subject global assessment and satisfaction questionnaire at the Final Visit.	The co-primary efficacy parameters, include inflammatory lesion counts and IGA, will be evaluated at Day 0/Baseline and at Weeks 4, 8, and 12 (Final Visit). The Subject Global Assessment will be performed at Weeks 2, 4, 8, and 12 (Final Visit). The subject satisfaction questionnaire will be assessed at Week 12 (Final Visit) only.	Addition of more frequent subject global assessments to be conducted at each post-Day 0/Baseline visit.
Table 1 Schedule of Study Assessments and Procedures – Study FX2016-12: Subject Global Assessment	Subject Global Assessment at Week 12 (Final Visit) only.	Additional Subject Global Assessments added at Weeks 2, 4, and 8.	Addition of more frequent subject global assessments to be conducted at each post-Day 0/Baseline visit.
Sect. 7.4; 7.5 and 7.6	New text.	Have the subject complete the Subject Global Assessment (Section 9.2.3)	As above.
Sect. 9.2.3	This score will be obtained from the subject at Visit 7 (Week 12/Final Visit) using the questionnaire in Appendix 1.	This score will be obtained from the subject at Visit 2 (Week 2), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/Final Visit) using the questionnaire in Appendix 1.	As above.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 6.2 Exclusion Criteria 23	Screening electrocardiogram (ECG) that reveals a QTcF >500 msec.	Text removed.	A review of Solodyn [®] product labelling and an assessment of the safety and pharmacokinetics of minocycline when topically applied as FMX101 (4% minocycline HCl foam) to moderate-to-severe acne vulgaris subjects under maximum use conditions (4g per day for 21 days) warrants the removal of ECG assessments at Day 0/Baseline as it has been determined by the Sponsor as being an unnecessary procedure.
Table 1 Schedule of Study Assessments and Procedures – Study FX2016-12	Electrocardiogram	Text removed.	As above.
Sect. 7.1 Screening Visit	Perform 12-lead ECG (Section 10.7.1)	Text removed.	As above.
Sect. 10.7.1 Electrocardiograms	A standard 12-lead ECG will be performed at Screening only. Subjects will be supine and at rest for at least 10 minutes before measurement. Subjects will have their participation discontinued if an ECG reveals a QTcF>500msec (see Exclusion Criterion 23).	Text removed.	As above.
Global change	Visit schedule has been adjusted from Visit 1 (Day 0/Baseline); Visit 2 (Week 1); Visit 3 (Week 4); Visit 4 (Week 6); Visit 5 (Week 8); Visit 6 (Week 10) and Visit 7 (Week 12/Final Visit)	New schedule is Visit 1 (Day 0/Baseline); Early Follow-up (Week 1); Visit 2 (Week 2); Visit 3 (Week 4); Visit 4 (Week 8) and Visit 5 (Week 12/Final Visit)	To remove unnecessary study visits.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 7.3 Early Follow-up, Week 1 (±3 Days)	New text.	7.3 Early Follow-up, Week 1 (±3 Days) An early follow-up telephone call will be made 1 week after Visit 1, Day 0/Baseline. Record concomitant medications (Section 8.7). Record Aes (Section 10.8). Confirm that subject continues to use only the provided facial cleanser and moisturizer. Review application instructions to confirm that the subject continues to use the study drug as directed. Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.	To support early contact with subjects to address outstanding questions and reinforce study instructions.
Sect. 7.7 Visit 5, Week 12 (-3/+5 days) / Final Visit or Early Termination	Schedule/confirm a safety follow-up telephone call 4 weeks from Visit 7/Week 12 (Final Visit) date (±5 days) for subjects that will <u>not</u> participate in study FX2015-13 (Open label study) (Section 7.9).	Schedule/confirm a safety follow-up telephone call 4 weeks from Visit 5/Week 12 (Final Visit) date (±5 days) only for subjects that will not participate in study FX2015-13 (Open label study) (Section 7.9) and presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit).	Clarification of Safety Follow telephone call requirements.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 7.8 Safety Follow-Up ((±5 days)	A safety follow-up telephone call will be made 4 weeks after Visit 7/Week 12 (Final Visit) for <u>only</u> those subjects that do not participate in study FX2015-13 (Open label study). Follow up on existing and any new concomitant medications and adverse events will be recorded.	A safety follow-up telephone call will be made 4 weeks after Visit 5/Week 12 (Final Visit) for <u>only</u> those subjects that do not participate in study FX2015-13 (Open label study) and presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit). Follow up on these adverse events and any new concomitant medications will be recorded.	Clarification of AE reporting requirements.
Synopsis, Diagnosis and Main Criteria for Inclusion	At least 12 and not more than 50 inflammatory facial lesions (ie, papules/pustules),...	At least 15 and not more than 75 inflammatory facial lesions (ie, papules/pustules),...	Change inflammatory lesion count range in the inclusion criteria from 12-50 to 15-75.
Sect. 6.1 Inclusion Criteria	a. At least 12 and not more than 50 facial papules and pustules...	a. At least 15 and not more than 75 facial papules and pustules...	As above.
Table 2 Study Drug Kits and Treatments – Study FX2016-12	Additional kits of 2 canisters may be dispensed at other visits if required.	Text removed.	Redundant text due to change in visit schedule
Sect. 8.1.1 Dosing Instructions	Additional kits will be available for dispensing at other visits (ie, Visits 4 and 6) to ensure enough product is available for daily dosing.	Text removed.	As above.
Sect. 12.2 Protocol Amendments	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	Text removed.	Misplaced text / repetition.

Section(s)	Revision		Rationale
	Old Text	New Text	
Appendix 3	New text.	Addition of investigator acknowledgement of protocol review and receipt.	Investigator confirmation of review and receipt of study protocol.

17.2 Amendment 2, effective May 12th, 2017

The following is the summary of the changes that were made to Protocol FX2016-12 Version 2 issued March 06, 2017.

Content changes:

New or changed text is **bolded**.

Section(s)	Revision		Rationale
	Old Text	New Text	
Synopsis, Sect. 5.1 Overall Study Design	Subjects will be assigned to 1 of 2 treatments according to the randomization schedule.	Subjects will be assigned to 1 of 2 treatments according to the randomization schedule, stratified by investigational site.	Addition of clarifying text.
Synopsis, Number of Subjects (planned), Sect. 6 Study Population	...approximately 600...	...approximately 750 ...	Adjustment in relation to a new sample size calculation.
Sect. 6.1 Inclusion Criteria	Subjects were included in the study if they met...	Subjects can be included in the study if they meet all...	Typographical error.
Sect. 6.2 Exclusion Criteria	Subjects were excluded from enrollment...	Subjects should be excluded from enrollment	As above.
Sect. 6.2 Exclusion Criterion 4	An active nodule on the face >5 mm in diameter.	Text removed.	Exclusion criterion inconsistent with IGA grade 4 inclusion criterion.
Sect. 7 Study Procedures	... Exclusion Criteria 11 and 12 , they must first enter...as specified in Exclusion Criteria 11 and 12 , respectively)...	...Exclusion Criteria 10 and 11 , they must first enter...as specified in Exclusion Criteria 10 and 11 , respectively)...	Reference changed due to renumbering of exclusion criteria due to the above omission.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 7 Study Procedures	...they must first enter a washout period (ie, 1 month or 2 weeks, as specified in Exclusion Criteria 10 and 11, respectively) before beginning the screening procedures.	...they must first enter a washout period (ie, 1 month or 2 weeks, as specified in Exclusion Criteria 10 and 11, respectively) during the screening period. Screening procedures are to be performed as defined in the schedule of events Table 1.	Clarification that prior medication wash-out can occur during the screening period.
Table 1 Schedule of Study Assessments and Procedures, Sect. 7.4 Visit 2, Week 2 (±3 Days), Sect. 8.1.1 Dosing Instructions	Procedure to dispense study drug at Visit 2.	Procedure removed.	Unnecessary dispensing occasion.
Synopsis, Study Duration, Sect. 7.7, Sect. 7.8, Table 1f	...FX2015-13...	...FX2016-13...	Incorrect study reference.
Table 2	...25 g...	... 35 g ...	Correction of canister content weight.
Table 2	Once daily application of a sufficient amount of foam to cover the involved area.	Once daily application of a sufficient amount of foam to cover the entire face.	Adjustment of application instructions to align with that conducted during Phase 2 study (FX2015-10).
Sect. 8.1.1 Dosing Instructions	...over all involved areas of the face. Additional drug may be used as needed to assure the entire involved area...	...over all areas of the face . Additional drug may be used as needed to ensure the entire face is treated ...	As above.
Sect. 5.1 Overall Study Design, Sect. 8.1.1 Dosing Instructions	Study drug should be applied at approximately the same time each day, preferably in the evening about 1 hour before bedtime.	Study drug should be applied at approximately the same time each day, about 1 hour before bedtime.	Removal of evening application preference to reflect subjects with different sleep patterns e.g. shift workers.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 11.2 Determination of Sample Size and Table 5 Sample Size Calculations Based on IGA Scores after CCI [REDACTED] of Treatment in Phase 2 Study FX2015- 10	N/A.	Simplification of Table 5 and inclusion of new sample size calculations.	Sponsor has elected to increase the sample size based on additional scenarios covering the Phase 2 study data (FX2015-10).
Sect. 9.3 Photography	New text.	Photography will be performed at selected study centers only. Study centers should refer to their specific Clinical Trial Agreement to confirm participation.	Clarification that not all study centers will participate in subject photography.
Table 1 Schedule of Study Assessments and Procedures	New table footer	† only for study centers participating in subject photography (Section 9.3).	As above.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 11.3 Analysis Populations	<p>Subjects may be excluded from the PP population if any of the following are met:</p> <p>Failure to meet inclusion/exclusion criteria</p> <p>Have administered any interfering concomitant medications</p> <p>Have not, in the opinion of the Investigator, been compliant with the treatment regimen (eg, reported frequent missed doses)</p> <p>Randomization error</p> <p>Prior to breaking the blind, additional criteria for exclusion from the PP population may be included to accommodate for unforeseen events that occurred during the conduct of the study.</p>	<p>Subjects may be included in the PP population if all of the following are met:</p> <p>Have met all inclusion/exclusion criteria</p> <p>Have not administered any interfering concomitant medications</p> <p>Were not subject to a randomization error</p> <p>Completed treatment through Week 12</p> <p>Were greater than 80% compliant with study medication where % compliance is defined as:</p> <p><i>% Compliance = 100 x (expected treatment duration in days minus # days a dose was missed) / (expected treatment duration in days)</i></p>	Request by FDA to clarify the Per Protocol population.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 11.5.1 Primary Efficacy Endpoints	The dichotomized IGA will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, stratified by investigational site.	<p>An investigation site-by-treatment interaction term will be included in the ANCOVA model to test for homogeneity among investigational sites.</p> <p>The dichotomized IGA will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, stratified by investigational site. For dichotomized IGA, the investigational site-by-treatment interaction will be assessed with the Breslow-Day test. Investigational site-by-treatment interaction will be tested at a two-sided 0.1 level, and if significant will be further explored through the examination of descriptive statistics by individual (non-pooled) investigative sites.</p> <p>For analysis purposes, all investigative sites with fewer than 8 randomized subjects will be combined into a single pooled site. If a resulting pooled site still has fewer than 10 randomized subjects, then this pooled site will be further combined with the smallest unpooled site. This pooling process will continue until there are at least 8 randomized subjects in each pooled site.</p>	Request by FDA to clarify the statistical approach for pooled site and site interaction analysis.

APPENDIX 1: Subject Global Assessment Questionnaire

Question: “Considering your rosacea just before starting treatment and considering your condition today, indicate the change you have experienced according to the scale below”:

- 5 = Much better than prior to treatment
- 4 = Slightly better than prior to treatment
- 3 = Same as prior to treatment
- 2 = Slightly worse than prior to treatment
- 1 = Much worse than prior to treatment

APPENDIX 2: Subject Satisfaction Questionnaire

The following 8 questions will be asked of the subject at Visit 5 (Week 12 / Final Visit):

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

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

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

The answer to Question 8 will be selected from the following:

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

APPENDIX 3: Acknowledgment Of Receipt And Review Of Protocol

Protocol Number: FX2016-12, Version 3

Protocol Title: A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (FX2016-12)

I hereby acknowledge receipt and review of the following Protocol:

1. Version 3, dated May 12th, 2017

Principal Investigator Name (Print)

Principal Investigator Signature

Date of Signature
(DD MMM YYYY)

CLINICAL PROTOCOL

Title Page

Study Title: A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (FX2016-12)


Sponsor: Foamix Pharmaceuticals, Inc.
520 US Highway 22, Suite 305
Bridgewater, NJ 08807

Protocol Identification: FX2016-12

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: Version 2 (Amendment 1)

Supersedes: Version 1, issued 20 Jan 2017

Prepared by: The Write Company, LLC

Confidentiality Statement

This document is the property of Foamix Pharmaceuticals, Inc., and is confidential and proprietary. The information contained herein is believed to be accurate and complete as of the date of preparation. The contents may not be used, divulged, published or otherwise disclosed without the expressed consent of Foamix Pharmaceuticals, Inc.

Signature Page

Title: A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (Study FX2016-12)

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:	A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (Study FX2016-12)	
Protocol No:	FX2016-12	
Study Centers:	Multicenter (approximately 40 sites in the USA)	
Publication (reference):	None	
Phase of Development:	3	
Objectives:	Primary Objectives: <ul style="list-style-type: none"> To determine the efficacy of FMX103 1.5% minocycline foam applied topically once daily for 12 weeks in the treatment of rosacea. To evaluate the safety of topical minocycline foam applied once daily for 12 weeks. 	
Study Design and Methods:	<p>This is a randomized, multicenter, double-blind, vehicle-controlled, 2-arm study to evaluate the safety and efficacy of FMX103 topical foam containing 1.5% minocycline compared to vehicle, in the treatment of subjects with moderate-to-severe facial papulopustular rosacea. Qualified subjects will be randomized in a 2:1 ratio (active:vehicle) to receive 1 of the following 2 treatments:</p> <ul style="list-style-type: none"> FMX103 minocycline foam 1.5% Vehicle foam <p>Subjects will be assigned to 1 of 2 treatments according to the randomization schedule. Subjects will apply (or have applied) the study drug topically once daily for 12 weeks as directed. Subjects will be advised to use the study drug at approximately the same time each day. Both the Investigator and subject will be blinded to the study drug identity.</p> <p>Subjects will return for visits at Weeks 2, 4, 8, and 12. Efficacy evaluations (inflammatory lesion counts and Investigator's Global Assessment [IGA] score) will be performed at Weeks 4, 8, and 12</p>	

	during the study.																		
Number of Subjects (planned):	The planned enrollment is approximately 600 male and female subjects. Subjects will be randomly assigned to the two treatment groups, FMX103 1.5% and vehicle, in a 2:1 ratio, respectively.																		
Diagnosis and Main Criteria for Inclusion:	<p>Healthy male or non-pregnant females, aged ≥18 years with a clinical diagnosis of moderate to severe facial papulopustular rosacea, defined as the presence of:</p> <ul style="list-style-type: none">At least 15 and not more than 75 inflammatory facial lesions (ie, papules/pustules), andAn IGA of rosacea severity of moderate or severe using the following scale: <table><tr><th>Score</th><th>Grade</th><th>Description</th></tr><tr><td>0</td><td>Clear</td><td>No inflammatory papules or pustules</td></tr><tr><td>1</td><td>Almost clear</td><td>Few inflammatory papules or pustules</td></tr><tr><td>2</td><td>Mild</td><td>Several inflammatory papules or pustules</td></tr><tr><td>3</td><td>Moderate</td><td>Moderate number of inflammatory papules or pustules and no nodules</td></tr><tr><td>4</td><td>Severe</td><td>Many inflammatory papules or pustules, and up to 2 nodules</td></tr></table> <ul style="list-style-type: none">Current or history of erythema and/or flushing <p>Subjects must be willing to minimize external factors that might trigger rosacea flare-ups (eg, spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, and alcoholic beverages).</p>	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
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																	
Test Product, Dose and Mode of Administration:	FMX103 minocycline foam 1.5%. Topical application, once daily to the face, for 12 weeks.																		
Reference Therapy:	Vehicle foam. Topical application, once daily to the face, for 12 weeks.																		
Study Duration:	Subject participation in the study will be up to 18 weeks: up to 6 weeks for Screening and Day 0/Baseline, and 12 weeks of study treatment. A safety follow-up telephone call will be conducted 4 weeks after completion of study treatment for <u>only</u> those subjects that do not participate in study FX2015-13 (Open label study) and who presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit).																		
Endpoints and Outcomes:	<p>Efficacy Evaluations</p> <p>The co-primary efficacy parameters, include inflammatory lesion counts and IGA, will be evaluated at Day 0/Baseline and at Weeks 4, 8, and 12 (Final Visit). The Subject Global Assessment will be performed at Weeks 2, 4, 8, and 12 (Final Visit). The subject satisfaction questionnaire will be assessed at Week 12 (Final Visit) only.</p> <p>Safety Evaluations</p> <p>The safety assessments will include adverse events (volunteered, observed, and elicited by general questioning in a non-suggestive manner), physical examinations, vital signs, clinical laboratory tests,</p>																		

	and local signs and symptoms assessments (including erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation) scores.
Statistical Methods:	<p>The primary population for efficacy analysis will be the intent-to-treat (ITT) population, using multiple imputations to impute missing values. Supportive efficacy analyses will be conducted on the per-protocol (PP) population, with no imputation for missing values.</p> <p>The co-primary efficacy endpoints will be the dichotomized IGA score where treatment success is defined as at least a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Week 12 compared to Day 0/Baseline and the absolute change in inflammatory lesion count at Week 12 compared to Day 0/Baseline.</p> <p>The key secondary endpoints will be analyzed hierarchically:</p> <ul style="list-style-type: none"> • Dichotomized IGA score where treatment success is defined as a 2-step improvement in score at Week 12 compared to Day 0/Baseline. • Percent change in inflammatory lesion count at Week 12 compared to Day 0/Baseline. <p>Continuous efficacy endpoints will be analyzed using analysis of covariance (ANCOVA). Dichotomized efficacy endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test.</p> <p>The tolerability and safety of topical minocycline foam applied daily for 12 weeks will be evaluated using summary statistics and individual subject data listings.</p> <p>The active treatment group will be tested against vehicle at the 0.05 two-sided level of significance. No statistical tests will be performed for any of the safety assessments.</p>

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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
BOCF	Baseline observation carried forward
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRO	Contract Research Organization
eCRF	Electronic case report form
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 System
ITT	Intent-to-treat (population)
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model for repeated measures
OC	Observed cases
OTC	Over-the-counter
PP	Per-protocol (population)
PT	Preferred term
RBC	Red blood cell
RDC	Remote data capture
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
US	United States
WBC	White blood cell




2

2 STUDY ADMINISTRATIVE STRUCTURE

Internal

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

External – Contract Research Organization (CRO)

Name	Affiliation / Address / Telephone Number	Responsibility
		

3 INTRODUCTION

Papulopustular rosacea is a chronic disorder affecting both the skin and the eye. 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.

Foamix has developed a topical minocycline foam product that is being evaluated for safety and efficacy in the treatment of rosacea. Minocycline hydrochloride is an established broad spectrum antibiotic that is used orally in the treatment of 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 has been evaluated in a Phase 2 study at two minocycline concentrations, 1.5% and 3%. The study included 232 subjects (males/females, aged ≥ 18 years) with moderate-to-severe papulopustular rosacea defined by the Investigator's Global Assessment (IGA) score and with ≥ 12 inflammatory facial lesions (papules/pustules) at Day 0/Baseline. Subjects were treated with FMX103 1.5%, FMX103 3%, or vehicle foam, once daily for 12 weeks. Efficacy and safety were evaluated at Weeks 2, 4, 8, and 12, with an additional safety follow-up visit at Week 16. The primary efficacy end point was the absolute change in inflammatory lesion count at Week 12. Other assessments included IGA improvement of ≥ 2 grades and reaching an IGA score of "clear" or "almost clear" (IGA 0/1), clinical assessment of erythema, and safety and tolerability.

At Week 12, both the 1.5% and 3% doses of FMX103 significantly reduced the number of papules and pustules vs. vehicle (both $p < 0.001$, intent-to-treat [ITT] population). The mean reduction in lesion count from Day 0/Baseline was 21.1 for the FMX103 1.5% dose, 19.9 for the FMX103 3% dose, and 7.8 for the vehicle. The corresponding percent reductions were 61.4% and 55.5% for the 1.5% and 3% doses, respectively, and 29.7% for the vehicle.

Both the 1.5% and 3% doses of FMX103 were statistically significantly better than vehicle in improving IGA scores by ≥ 2 grades at week 12 ($p = 0.002$ and $p = 0.032$, respectively). Both doses were also statistically significantly better than vehicle in achieving an IGA of "clear or almost clear" (score 0/1) at Week 12 ($p = 0.001$ and $p = 0.041$, respectively). Both FMX103 1.5% and 3% doses appeared to be generally safe and well-tolerated. Treatment-related dermal reactions were reported in 1 subject from the FMX103 1.5% dose group (considered mild) and in a few subjects

from the FMX103 3% dose group (mild, n=1; moderate, n=2; severe, n=1). No treatment-related systemic adverse events (AEs) were reported and discontinuation due to AEs (eczema, n=1; rosacea, n=1; burning sensation, n=1) was reported in 3 subjects in the FMX103 3% dose group.

As a consequence of the above, the FMX103 1.5% dose concentration has been selected for further development. This Phase 3 study will further assess the safety and efficacy of topical minocycline HCl foam, 1.5%, applied once daily compared with vehicle foam for the treatment of moderate-to-severe papulopustular rosacea.

4 STUDY OBJECTIVES

The primary objectives of the study are:

- To determine the efficacy of FMX103 1.5% minocycline foam applied topically once daily for 12 weeks in the treatment of rosacea.
- To evaluate the tolerability and safety of topical minocycline foam applied once daily for 12 weeks.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is a randomized, multicenter, double-blind, vehicle-controlled, 2-arm study to evaluate the safety and efficacy of FMX103 topical foam containing 1.5% minocycline compared to vehicle, in the treatment of subjects with moderate-to-severe facial papulopustular acne rosacea.

Qualified subjects will be randomized in a 2:1 ratio (active:vehicle) to use once daily one of the following two treatments:

- FMX103 minocycline foam 1.5%
- Vehicle foam

Subjects will be assigned to 1 of 2 treatments according to the randomization schedule. Subjects will apply (or have applied) the study drug topically once daily for 12 weeks as directed. Subjects will be advised to use the study drug at approximately the same time each day, preferably in the evening about 1 hour before bedtime. Both the Investigator and subject will be blinded to the study drug identity.

Subjects will return for visits at Weeks 2, 4, 8, and 12. Efficacy evaluations (inflammatory lesion counts [\[Section 9.1.1\]](#) and IGA score [\[Section 9.1.2\]](#)) will be performed at Weeks 4, 8, and 12 during the study. Other assessments will be performed as described in [Section 9](#) and [Section 10](#).

5.2 Rationale for Study Design and Dose Selection

A randomized, multicenter, double-blind, vehicle-controlled study design has been selected in order to assess the efficacy of the study drug. The subjects will be selected according to predefined entry criteria. The study treatment duration of 12 weeks is expected to be sufficient to show a treatment effect.

The concentration of minocycline in the composition was selected according to formulation integrity and stability considerations and based on the results of Phase 2 Study FX2015-10 (described above in [Section 3](#)).

Because of the mode of action of tetracycline drugs, the primary efficacy endpoints will be the effect on inflammatory lesion counts and IGA scores ([Section 9](#)).

6 STUDY POPULATION

The study will randomize approximately 600 subjects to active or vehicle treatment (in a 2:1 ratio) at approximately 40 sites in the US.

6.1 Inclusion Criteria

Subjects were included in the study if they met all of the following inclusion criteria at the time of enrollment:

1. Male or female ≥ 18 years-of-age.
2. Moderate-to-severe rosacea (as per the IGA score; [Table 3](#)) on the proposed facial treatment area consisting of:
 - a. At least 15 and not more than 75 facial papules and pustules, excluding lesions involving the eyes and scalp;
 - b. No more than 2 nodules on the face.
3. Presence of or history of erythema and/or flushing on the face.
4. If a female 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.
5. Willing to minimize external factors that might trigger rosacea flare-ups (eg, spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, and alcoholic beverages).
6. Subjects who use make-up must have used the same brands/types of make-up for a minimum period of 14 days prior to study entry and must agree to use the same make-up, brand/type, or frequency of use, throughout the study.
7. Completed and signed an appropriately administered Informed Consent Form (ICF) prior to any study-related procedures.

6.2 Exclusion Criteria

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

1. Woman who is pregnant, lactating, or planning to become pregnant during the study period.
2. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea.

3. Moderate or severe rhinophyma, dense telangiectasia (score 3, severe; [Section 10.7.2.2](#)), or plaque-like facial edema.
4. An active nodule on the face >5 mm in diameter.
5. Excessive facial hair (eg, beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.
6. History of hypersensitivity or allergy to minocycline, any other tetracycline, or of any other component of the formulation.
7. Severe erythema, dryness, scaling, pruritus, stinging/burning, or edema.
8. Active ocular rosacea (eg, conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics.
9. Use within 6 months prior to Day 0/Baseline of oral retinoids (eg, Accutane[®]) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
10. Initiation of use of estrogens or oral contraceptives less than 3 months prior to Day 0/Baseline.
11. Use within 1 month prior to Day 0/Baseline of:
 - a. Topical retinoids to the face.
 - b. Systemic antibiotics known to have an impact on the severity of facial rosacea (eg, containing tetracycline and its derivatives, erythromycin and its derivatives, sulfamethoxazole, or trimethoprim). Subjects requiring systemic antibiotics not known to affect rosacea will be considered on a case-by-case basis.
 - c. Systemic corticosteroids (Note: intranasal and inhalational corticosteroids do not require a washout and maybe used throughout the trial if the subject is on a stable dose).
12. Use within 2 weeks prior to Day 0/Baseline of:
 - a. Topical corticosteroids.
 - b. Topical antibiotics.
 - c. Topical medications for rosacea (eg, metronidazole).
13. Use of a sauna during the 2 weeks prior to Day 0/Baseline and during the study.
14. Had wax epilation of the face within 2 weeks prior to Day 0/Baseline.
15. Active bacterial folliculitis.
16. Consumption of excessive alcohol, abuse of licit or illicit drugs, or a condition that, in the opinion of the Investigator, could compromise the subject's ability to comply with study requirements.
17. Participation in activities that involve excessive or prolonged exposure to sunlight or weather extremes, such as wind or cold.

18. Presence of any clinically significant condition or situation, other than the condition being studied, that in the opinion of the Investigator would interfere with the study evaluations or optimal participation in the study.
19. Participation in an investigational drug study (ie, subject has been treated with an investigational drug) within 30 days prior to Day 0/Baseline. Subjects who are participating in non-treatment studies such as observational studies or registry studies can be considered for inclusion.
20. Previously enrolled in this study.
21. Prior laser therapy (for telangiectasia or other conditions), electrodesiccation, or phototherapy (eg, ClearLight[®]) to the facial area within 180 days prior to Day 0/Baseline.
22. Prior cosmetic procedures (eg, facials) that may affect the efficacy and safety profile of the investigational product within 14 days prior to Day 0/Baseline.

7 STUDY PROCEDURES

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

The eligible subject who is willing to participate in the study will then sign an appropriately administered ICF prior to any study-related procedures being performed.

Procedures at the Screening Visit will include obtaining blood and urine samples for clinical laboratory tests. The results of these tests must be no more than 45 days old at the time of the Day 0/Baseline Visit and randomization.

If a subject who has agreed to participate in the study and signed the ICF is currently undergoing rosacea therapy identified in Exclusion Criteria 11 and 12, they must first enter a washout period (ie, 1 month or 2 weeks, as specified in Exclusion Criteria 11 and 12, respectively) before beginning the screening procedures.

The schedule of study assessments and procedures and the time point at which they will be performed during the study is presented in Table 1. If a subject prematurely withdraws from the study, the subject should return to the study site for an early termination visit during which all evaluations described under Final Visit 5/Week 12 must be performed.

Table 1 Schedule of Study Assessments and Procedures – Study FX2016-12

Assessment or Procedure	Screening	Day 0 / Baseline ⁰	Visits/Early Follow-up				Final Visit ^b	Safety Follow-up ^f
			EF	2	3	4		
Visit		1	1	2	4	8	12	
Informed consent	X							
Demographic data	X							
Assign subject identification	X							
Medical/surgical/medication history	X							
Inclusion/exclusion criteria	X	X						
Physical examination, height, weight ^c		X					X	
Blood pressure/heart rate ^d		X		X	X	X	X	
Blood and urine samples for clinical laboratory tests	X						X	
Urine pregnancy test (females of childbearing potential only)	X	X			X	X	X	
Lesion counts	X	X			X	X	X	
Investigator's Global Assessment	X	X			X	X	X	
Subject Global Assessment				X	X	X	X	
Subject Satisfaction Questionnaire							X	
Local signs and symptoms assessments ^e	X	X		X	X	X	X	
Photography		X			X	X	X	
Randomization		X						
Concomitant medications		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Perform drug accountability				X	X	X	X	
Collect used drug canister(s)				X	X	X	X	
Dispense study drug		X		X	X	X		
Schedule/confirm next visit	X	X	X	X	X	X		

EF – Early Follow-up telephone call, no visit

- Day 0/Baseline must occur within 45 days of Screening. Blood test results must not show clinically significant abnormalities.
- If a subject prematurely withdraws from the study, all evaluations described under Visit 5/Week 12 (Final Visit) must be performed at an Early Termination Visit.
- Height to be measured only at Day 0/Baseline.
- Measure blood pressure and heart rate after the subject has been sitting for at least 5 minutes at rest.
- 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.
- A safety follow-up telephone call will be made 4 weeks after Visit 5/Week 12 (Final Visit) for only those subjects that do not participate in study FX2015-13 (Open label study) and presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit).

7.1 Screening Visit

- Obtain a signed and dated, written ICF prior to any study-related procedures.
- Obtain demographic data.
- Using the Interactive Response Technology System (IRT), assign the subject an identification number.
- Obtain medical/surgical history ([Section 10.1](#)).
- Obtain history of prior medication usage (including previous use of rosacea medications); record start and stop dates of any medications used in the last 3 months ([Section 10.2](#)).
- Assess eligibility according to the inclusion ([Section 6.1](#)) and exclusion criteria ([Section 6.2](#)).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test ([Section 10.6.1](#)).
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory ([Section 10.6.2](#)).
- Perform facial lesion count of inflammatory lesions ([Section 9.1.1](#)).
- Perform IGA ([Section 9.1.2](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Schedule/confirm the next study visit.

7.2 Visit 1, Day 0/Baseline Visit

- Confirm eligibility according to the inclusion ([Section 6.1](#)) and exclusion criteria ([Section 6.2](#)).
- Perform physical examination including height and weight ([Section 10.5](#)).
- Measure blood pressure and heart rate ([Section 10.4](#)).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test ([Section 10.6.1](#)).
- Perform facial lesion count of inflammatory lesions ([Section 9.1.1](#)).
- Perform IGA ([Section 9.1.2](#)).
- Perform photography ([Section 9.3](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Randomize the subject using the IRT when all criteria have been met.
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Dispense one kit (2 canisters) of study drug.

- Dispense facial cleanser and moisturizer.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.3 Early Follow-up, Week 1 (±3 Days)

An early follow-up telephone call will be made 1 week after Visit 1, Day 0/Baseline.

- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Confirm that subject continues to use only the provided facial cleanser and moisturizer.
- Review application instructions to confirm that the subject continues to use the study drug as directed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.4 Visit 2, Week 2 (±3 Days)

- Measure blood pressure and heart rate ([Section 10.4](#)).
- Have the subject complete the Subject Global Assessment ([Section 9.2.3](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Confirm that subject continues to use only the provided facial cleanser and moisturizer.
- Review application instructions to confirm that the subject continues to use the study drug as directed.
- Perform drug accountability to assess compliance ([Section 8.2](#)).
- Collect used study canister (if applicable).
- Dispense one kit (2 canisters) of study drug.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.5 Visit 3, Week 4 (±3 Days)

- Measure blood pressure and heart rate ([Section 10.4](#)).
- 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 9.2.3).
- Perform photography (Section 9.3).
- Perform local signs and symptoms assessments (Section 10.7.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test (Section 10.6.1).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.8).
- Perform drug accountability to assess compliance (Section 8.2).
- Collect used study drug canister (if applicable).
- Dispense one kit (2 canisters) of study drug.
- Confirm that subject continues to use only the provided facial cleanser and moisturizer and dispense additional quantities as required.
- Review application instructions to confirm that the subject continues to use the study drug as directed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.6 Visit 4, Week 8 (±3 Days)

- Measure blood pressure and heart rate (Section 10.4).
- 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 9.2.3).
- Perform photography (Section 9.3).
- Perform local signs and symptoms assessments (Section 10.7.2).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test (Section 10.6.1).
- Record concomitant medications (Section 8.7).
- Record AEs (Section 10.8).
- Perform drug accountability to assess compliance (Section 8.2).
- Collect used study drug canister (if applicable).
- Dispense one kit (2 canisters) of study drug.

- Confirm that subject continues to use only the provided facial cleanser and moisturizer and dispense additional quantities as required.
- Review application instructions to confirm that the subject continues to use the study drug as directed.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.7 Visit 5, Week 12 (-3/+5 days) / Final Visit or Early Termination

- Perform physical examination including weight ([Section 10.5](#)).
- Measure blood pressure and heart rate ([Section 10.4](#)).
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory ([Section 10.6.2](#)).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test ([Section 10.6.1](#)).
- Perform facial lesion count of inflammatory lesions ([Section 9.1.1](#)).
- Perform IGA ([Section 9.1.2](#)).
- Perform photography ([Section 9.3](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Have the subject complete the Subject Global Assessment ([Section 9.2.3](#)).
- Have the subject complete the Subject Satisfaction Questionnaire ([Section 9.2.4](#)).
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Collect all used and full study drug canisters.
- Perform drug accountability to assess compliance and record the date of the last dose ([Section 8.2](#)).
- Schedule/confirm a safety follow-up telephone call 4 weeks from Visit 5/Week 12 (Final Visit) date (± 5 days) only for subjects that will not participate in study FX2015-13 (Open label study) ([Section 7.9](#)) and presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit).

7.8 Safety Follow-Up (± 5 days)

A safety follow-up telephone call will be made 4 weeks after Visit 5/Week 12 (Final Visit) for only those subjects that do not participate in study FX2015-13 (Open label study) and presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit). Follow up on these adverse events and any new concomitant medications will be recorded.

8 STUDY TREATMENTS

This study will include FMX103 minocycline foam 1.5% and vehicle foam.

8.1 Treatments Administered

The description of study drug kits and treatments is shown below in [Table 2](#).

Table 2 Study Drug Kits and Treatments – Study FX2016-12

Dosage form description:	Foam containing minocycline HCl 1.5% or vehicle foam
Package description:	Canisters, each containing 25 g of the clinical trial supply foam
Daily dose:	Once daily 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) or 0.0 mg (vehicle) of minocycline.
Cumulative maximal dose for dosing (12 weeks):	630 mg (1.5%) minocycline
Dispensing:	Kits consisting of 2 canisters, each canister containing 25 g of FMX103 minocycline formulation, 1.5%, or vehicle dispensed at Visit 1 (Day 0/Baseline), Visit 2 (Week 2), Visit 3 (Week 4), and Visit 4 (Week 8).

8.1.1 Dosing Instructions

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

Study drug kits containing 2 canisters of investigational drug will be dispensed at Visit 1 (Day 0/Baseline), Visit 2 (Week 2), Visit 3 (Week 4), and Visit 4 (Week 8).

After shaking the canister well, a small amount of study drug (about ½ gram or a cherry-sized amount) should be expressed from the canister onto the finger tips and then applied as a thin layer over all involved areas of the face. Additional drug may be used as needed to assure the entire involved area is treated.

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

8.1.2 Manufacturer

The manufacturer of the investigational product is ASM Aerosol-Service AG, Moehlin, Switzerland.

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% and vehicle canisters must be stored at 2°C – 8°C until being dispensed to the subject. Subsequently, they must be stored at 20°C – 25°C (refer to USP Controlled Room Temperature). 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 use of the study drug. The Investigator or designee will verify the contents of the drug shipment and confirm receipt of the study drug in the 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 bottles of study drug will be returned to the Sponsor or designee by the time of the site's close-out visit. Receipt, distribution, and return of the study drug must be properly documented on forms provided by the Sponsor or designee.

8.4 Method of Assignment of Study Drug

After pretreatment clinical evaluations and all other Screening procedures have been completed, authorized site personnel will acknowledge that the applicable subject met all the specified inclusion criteria ([Section 6.1](#)) and none of the exclusion criteria ([Section 6.2](#)). Assignment to a treatment group will then follow a predetermined list of randomization numbers, with each successive number receiving 1 of the 2 treatments in random order. Authorized site personnel will use the IRT system to assign a kit number that corresponds to the randomization schedule. The kit box with the assigned kit number will be dispensed to the subject.

The randomization code will be provided by Premier Research, Research Triangle Park, NC.

8.5 Selection and Timing of Doses in the Study

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

8.6 Blinding

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

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

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

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

If unblinding is necessary, the subject will be withdrawn from the study and Early Termination Visit (ie, Visit 5 [Week 12]) assessments will be completed.

8.7 Prior/Concomitant Therapy

As necessary, subjects should use the facial cleanser *Cetaphil Gentle Skin Cleanser* and the facial moisturizer *Eucerin Daily Protection Broad Spectrum SPF30 Face Lotion*. Both products will be provided by the Sponsor. Alternative, non-medicated cleansers or moisturizers may be used if agreed to by the Sponsor.

The use of or change in the dose of any and all 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. Therapies (medication and non-medication therapies) not restricted by the protocol may be used. Non-prohibited chronic therapies being used at Day 0/Baseline may be continued. If a female subject is using an oral contraceptive product, she should have been on the same product for at least 3 months and she should continue using the same or equivalent product for the duration of the study.

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

All topical or systemic medications listed in the exclusion criteria are prohibited during this study. Similarly, no other topical medications are permitted to be used on the face during this period.

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 is not postmenopausal (defined as amenorrhea >12 consecutive months). Females of childbearing potential must have a negative urine pregnancy test and, if they are sexually active or become sexually active during the study, must use an effective method of birth control such as those listed below during the course of the study. The following is not an all-inclusive list; the subject must discuss with the Investigator the most appropriate form of birth control:

- Hormonal methods
 - Oral contraceptives – (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 kits (empty/used/unused) at the appropriate visits. The study site personnel will question the subject on the history of study drug use since the last visit. A subject who deviates significantly from the prescribed dosage will be counseled.

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 Co-Primary Efficacy Assessments

The co-primary efficacy assessments will include the inflammatory lesion counts and the IGA of severity of disease. Lesion counts, IGA, and other efficacy evaluations 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 will be performed at Screening and Visit 1 (Day 0/Baseline) to confirm eligibility, and again at Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/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 will be performed at Screening and Visit 1 (Day 0/Baseline) to confirm eligibility, and again at Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/Final Visit).

Table 3 IGA Scale for Rosacea – Study FX2016-12

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 [REDACTED] CCI Efficacy Assessments

9.2.1 Percent Change in Inflammatory Lesion Counts

The percent change in inflammatory lesion counts at Visit 5 (Week 12/Final Visit) compared to Visit 1 (Day 0/Baseline) will be evaluated.

9.2.2 Interim Change in Inflammatory Lesion Counts

The absolute [REDACTED] CCI change in inflammatory lesion counts at Visit 3 (Week 4) and Visit 4 (Week 8) compared to Visit 1 (Day 0/Baseline) will be evaluated.

9.2.3 Subject Global Assessment

This score will be obtained from the subject at Visit 2 (Week 2), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/Final Visit) using the questionnaire in [Appendix 1](#).

9.2.4 Subject Satisfaction Questionnaire

A subject satisfaction questionnaire ([Appendix 2](#)) will be administered at Visit 5 (Week 12/Final Visit).

9.3 Photography

Photography of the full face will be performed at Day 0/Baseline and at Weeks 4, 8, and 12 using recognized methods. The equipment and techniques for this photography and for archiving the images are described in the Study Manual. Photographs will be reviewed at the site and by the sponsor for quality. Photographs will not be used to assess the lesion counts or the IGA, but will be archived to be available for subsequent review, if required, by the sponsor, auditors, or the FDA.

10 SAFETY ASSESSMENTS

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

10.1 Medical/Surgical History

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

10.2 Medication History

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

10.3 Concomitant Medications

All topical or systemic medications listed in the exclusion criteria are prohibited. No other topical medications are permitted to be used on the face. All medication that the subject is currently taking or any change in medication or dosage since the last visit will be documented throughout the study. The use of or change in the dose of any and all concomitant medication, either prescription or 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.

10.4 Vital Signs

Heart rate and blood pressure (BP) will be measured at all post-Day 0/Baseline 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.

10.5 Physical Examination

A complete physical examination (excluding the genitourinary examination) will be performed.

Weight will be recorded at the Visit 1 (Day 0/Baseline) and Visit 5 (Week 12/Final Visit). Height will be measured at Visit 1 (Day 0/Baseline) only.

10.6 Clinical Laboratory Tests

Serum chemistry, hematology and urinalysis will be evaluated at the Screening Visit and Visit 5 (Week 12/Final Visit). All clinical laboratory tests will be performed at 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 FX2016-12

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

10.6.1 Urine Pregnancy Test

A urine pregnancy test will be performed on all females of childbearing potential at the Screening Visit, Visit 1 (Day 0/Baseline), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/Final Visit) or when a subject prematurely withdraws from the study.

10.6.2 Sample Collection, Storage, and Shipping

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

10.7 Other Safety Measurements

10.7.1 Local Signs and Symptoms Assessments

The severity of each of the following local signs and symptoms will be measured at Screening, Visit 1 (Day 0/Baseline), and at each study visit: 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 medication or is the reason for discontinuation from the study.

10.7.1.1 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

10.7.1.2 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

10.7.1.3 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

10.7.1.4 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

10.7.1.5 Dryness/Xerosis

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

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

10.7.1.6 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

10.7.1.7 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

10.7.1.8 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

10.8 Adverse Events

10.8.1 Method of Determining Adverse Events

Safety assessments will include recording AEs reported spontaneously by the subject or observed by the Investigator. AEs will be recorded at each visit on the appropriate CRF. Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded 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 10.8.4](#)) and recorded in the subject's source documents, and the results will be provided to the Sponsor.

For AE definitions and reporting requirements, refer to [Section 10.8.2](#) and [Section 10.8.3](#), respectively.

10.8.2 Adverse Event Definitions

10.8.2.1 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.

10.8.2.2 Serious Adverse Events

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

- Results in death.
- Is life-threatening.

(Note: The term “life-threatening” refers to any AE that, as it occurs, puts the subject at immediate risk of death. It does not refer to an AE that hypothetically might have caused death if it were more severe.)

- Results in hospitalization or prolongation of current hospitalization (not including hospitalization for a pre-existing condition that has not increased in severity or frequency from the subject’s underlying medical condition prior to entry into the study).
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect in the offspring of a subject.
- Is another serious (important medical events) 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.

10.8.2.3 Severity of Adverse Events

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

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

10.8.2.4 Relationship of Adverse Events to Study Treatments

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

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

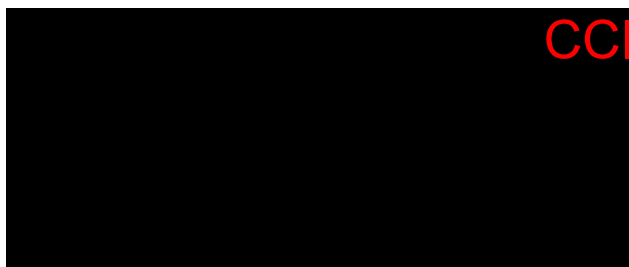
10.8.2.5 Adverse Events Expectedness

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.

10.8.3 Reporting Adverse Events

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

Any SAEs occurring in a subject receiving study drug must be reported to the Sponsor or designee within 24 hours of the site being informed of the event, even if the event does not appear to be drug-related. The report must be done by faxing the completed SAE Report Form to the Sponsor or designee. Any pertinent follow-up information should be provided in a similar manner. Contact information is provided below:



10.8.4 Adverse Event Follow-up

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

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

10.8.4.1 Pregnancy Reporting

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

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

A urine pregnancy test will be performed on all females of childbearing potential as described in [Section 10.6.1](#).

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, missed or late menstrual period). If a subject or Investigator suspects that the subject may be pregnant at any time before or during the study, the study drug must be withheld until the results of laboratory pregnancy testing are available. The Sponsor and site monitor must be notified and 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.

10.8.5 Clinically Significantly Abnormal Laboratory Results

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

10.9 Appropriateness of Safety Measurement

The safety assessments to be utilized 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 (SAP) will be finalized prior to breaking of the study blind.

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

11.2 Determination of Sample Size

In the Phase 2 Study FX2015-10, the proportion of subjects with an IGA score of 0 or 1 after [REDACTED] of treatment was [REDACTED] in the FMX103 1.5% dose group compared to [REDACTED] for the vehicle dose group. Table 5 provides alternate assumptions on this primary response criterion with corresponding implications on sample size. Power was set to 90% and a type-1 error was set to a two-sided test with a 0.05 level of significance. Sample size was calculated based on Fisher's Exact test.

Table 5 Sample Size Calculations Based on IGA Scores after [REDACTED] of Treatment in Phase 2 Study FX2015-10

Vehicle IGA (Score 0,1)	FMX103 1.5% IGA (Score 0,1)	Sample Size (Vehicle, Active)
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Assuming a [REDACTED] dropout rate, 400 subjects receiving FMX103 and 200 subjects receiving vehicle will provide at least 90% power for a statistically significant difference on an IGA score of 0 or 1.

For the co-primary endpoint of change from Day 0/Baseline to [REDACTED] in inflammatory lesion count, in the Phase 2 study the FMX103 1.5% dose group had a mean reduction of [REDACTED] lesions whereas the vehicle had a mean reduction of [REDACTED] lesions. The standard deviation was [REDACTED]. For a 90% power, [REDACTED] and [REDACTED] subjects in the FMX103 1.5% and vehicle groups, respectively, will be needed. Therefore, the sample size needed to provide at least 90% power for both co-primary endpoints is [REDACTED] and [REDACTED] subjects in the FMX103 1.5% and vehicle groups, respectively.

11.3 Analysis Populations

The following populations will be defined for analysis:

- Intent-to-Treat (ITT) population: all randomized subjects.
- Per-Protocol (PP) population: defined as the subset of the ITT population without any protocol deviations that may have an impact on the efficacy assessments. Subjects to be included in the PP population will be determined by the Sponsor/CRO prior to the unblinding of the study.

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

- Failure to meet inclusion/exclusion criteria
- Have administered any interfering concomitant medications
- Have not, in the opinion of the Investigator, been compliant with the treatment regimen (eg, reported frequent missed doses)

- Randomization error

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

- Safety Population: all randomized subjects who use any study product. Subjects who have no post-Day 0/Baseline assessments will be included in the Safety population unless all dispensed study drug is returned unused.

The ITT population will be the primary population for efficacy analysis. The PP population will be secondary for the co-primary endpoints only. The Safety population will be used for the analyses of safety endpoints.

All efficacy analyses will be conducted according to the randomized treatment assignment; all safety analyses will be conducted according to the treatment actually received.

11.4 Subject Accounting, Demographics, and Day 0/Baseline Characteristics

Demographics, Day 0/Baseline characteristics, and prior and concomitant medications will be summarized by treatment. Study completion status and reasons for discontinuation will also be displayed by treatment.

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

11.5 Efficacy Endpoints

The primary population for all efficacy analyses will be the ITT population. For the analyses of the co-primary and secondary efficacy endpoints based on the ITT population, a variety of methods will be used to impute missing data, including multiple imputation (MI), last-observation-carried forward (LOCF), and Day 0/Baseline observation carried forward (BOCF). MI will be the primary imputation method. Sensitivity analyses using LOCF and BOCF will be performed only on the co-primary efficacy endpoints to assess the robustness of alternate imputation assumptions. For the continuous efficacy measure, a mixed effects model for repeated measures (MMRM) analysis will also be conducted as a sensitivity analysis. All supportive analyses using the PP population will use the Observed-Cases (OC) approach, that is there will be no imputation for missing data at any time point. No other imputations will be made unless otherwise specified.

For all efficacy analyses, subjects will be analyzed according to the treatment group to which they were randomized.

11.5.1 Primary Efficacy Endpoints

The co-primary efficacy endpoints are:

- The absolute change in the inflammatory lesion count at Week 12 compared to Day 0/Baseline.
- The dichotomized IGA score where treatment success is defined as at least a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Week 12 compared to Day 0/Baseline.

The null hypothesis of the equality of the FMX103 1.5% and vehicle means for absolute change from Day 0/Baseline to Week 12 in the inflammatory lesion count and the equality of IGA success rates at Week 12 will each be tested at a two-sided 0.05 level of significance. Change from Day 0/Baseline in inflammatory lesion count will be analyzed using an analysis of covariance (ANCOVA), with treatment as a main effect, Day 0/Baseline inflammatory lesion count as a covariate, and investigational site as a blocking factor. Investigational site-by-treatment interaction will be tested at a two-sided 0.1 level, and if significant, will be further explored. The dichotomized IGA will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, stratified by investigational site.

11.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The dichotomized IGA score where success is defined as a 2-step improvement in score at Week 12 compared to Day 0/Baseline.
- The percent change in inflammatory lesion count at Week 12 compared to Day 0/Baseline.
- The absolute change from Day 0/Baseline in the inflammatory lesion count and IGA treatment success at the interim visit at Week 8.
- The absolute change from Day 0/Baseline in the inflammatory lesion count and IGA treatment success at the interim visit at Week 4.

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

11.5.3 [REDACTED] CCI

[REDACTED] CCI

- [REDACTED] CCI
- [REDACTED] CCI

11.6 Safety Endpoints

Safety endpoints will be reported on the Safety population. Subjects will be reported according to the treatment they actually received. Safety assessment will be based on descriptive statistics

and individual 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 pre-treatment, or worsen relative to the pre-treatment state. Summaries of AEs will be limited to TEAEs. The number and percentage of subjects reporting events under each System Organ Class (SOC) and preferred term (PT) will be summarized for each treatment group. At each level of summarization, a subject will be counted only once if he/she reported one or more events. The severity of TEAEs and relationship to study drug will be summarized in a similar manner. For summaries of relationship to study drug, a subject will be classified according to the closest relationship. For summaries of TEAE severity, a subject will be classified according to the highest severity.

TEAEs, vital signs, and clinical laboratory measurements will be summarized by treatment group using descriptive statistics. For vital signs, change from Day 0/Baseline values will also be summarized. For all safety variables, subject data listings will be provided.

Local signs and symptoms 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 10.7.2](#).

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 prematurely withdraw from the study 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 Day 0/Baseline and at each post-Day 0/Baseline time point. Changes from Day 0/Baseline will also be summarized. Day 0/Baseline is defined as the last non-missing value prior to the first dose of study drug.

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 Day 0/Baseline with the number of subjects with low, normal, or high values at the Final Visit. Day 0/Baseline is defined as the last non-missing value prior to the first dose of study drug.

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

11.7 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 immediately notify the Sponsor of any regulatory authority inspections. The Investigator will be informed about the outcome of any Sponsor audit.

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

Monitoring visits will take place on a regular basis according to the enrollment rate and number of subjects enrolled at each investigational site. During these visits, the monitor will check the completion of the CRF entries, compliance with the study protocol and with GCP-ICH, and their agreement with the source data. The monitor will also verify the correct use of the study drug. At a 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 the IRB's guidelines.

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

12.4 Withdrawal of Subjects

Withdrawn subjects are those who do not complete all evaluations and procedures outlined in the protocol. Subjects who discontinue taking study drug for any reason must also be withdrawn from the study. Subjects may be withdrawn from the study because of 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 10.8.4](#).
- **Abnormal Laboratory Result:** Any clinically significant laboratory abnormality that requires withdrawal of the subject from the study should be considered an AE leading to withdrawal. If possible, laboratory tests will be repeated for any results that were clinically significantly abnormal until the abnormality is resolved or stabilized to the satisfaction of the Investigator in consultation with the medical monitor.
- **Lost to Follow-up:** Confirmed at minimum by two phone calls and a traceable letter without answer.
- **Subject Request:** Subject requests, for any reason (eg, AE), to be withdrawn or withdraws his/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, relocation of subject, etc. If a subject becomes pregnant during the study, the subject will be withdrawn from the study and followed through conclusion of the pregnancy.

If a subject is withdrawn from the study following the start of study drug, all Visit 5 (Week 12/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, which will make reasonable efforts to assure that the results are published in a peer-reviewed journal. As some of the information concerning the investigational product and development activities at the Sponsor

may be of a strictly confidential 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 (IRB)

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/her entry into the study (ie, before examinations and procedures associated with selection for the study are initiated). Each subject will have ample opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Following this informative discussion, the subject will be asked if he/she is willing to sign a statement of informed consent. Only subjects who voluntarily sign the ICF may enter the study.

The ICF must be reviewed and approved by the Sponsor and the IRB prior to their 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/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 ensures that the following have permission to review all study-related documents: monitor, auditor, IRB, and regulatory authorities. The subject's identity and study-related records

will remain confidential throughout the duration of the study data collection and reporting process.

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

13.6 Financing

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

Completion of Financial Disclosure Forms will be required before the study starts. Any additions to the primary site personnel will necessitate the completion of new Financial Disclosure Forms. This information will also be collected at site closure and 1 year after the completion of the study.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and 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 (CQA) Department may conduct periodic audits of the study processes, including, but not limited to, auditing the clinical site, laboratories, vendors and CROs, the clinical database, and the final study report.

15 DATA HANDLING AND RECORD KEEPING

This study will use web-based, electronic case report forms (eCRFs) developed through a validated, Electronic Records/Electronic Signatures-compliant platform (US Title 21 CFR Part 11). Foamix Clinical Data Management department or designee will create the 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 FX2016-12.

Section 17.1 describes the changes made to Protocol FX2016-12 Version 1 issued January 20, 2017, via Amendment 1 effective March 6th, 2017.

17.1 Amendment 1, effective March 6th, 2017

The following is the summary of the changes that were made to Protocol FX2016-12 Version 1 issued January 20, 2017.

Content changes:

New or changed text is **bolded**.

Section(s)	Revision		Rationale
	Old Text	New Text	
Synopsis (Study Centers); Sect. 6 Study Population	...approximately 30 sites...	...approximately 40 sites...	Number of study centers adjusted to account for larger study sample size.
Sect. 11.2 Determination of Sample Size; Table 5 Sample Size Calculations Based on IGA Scores after CCl of Treatment in Phase 2 Study FX2015-10 and text	... CCl CCl ...	Typographic error.
Sect. 11.2 Determination of Sample Size; Table 5 and text	New text inserted in Table 5.	Vehicle IGA (Score 0,1): CCl; FMX103 1.5% IGA (Score 0,1): CCl; Sample Size (Vehicle, Active): CCl	Study sample size calculation based on an assumed CCl reduction in effect difference between active and vehicle, relative to Study FX2015-10 FMX103 1.5% IGA (Score 0,1) v's Vehicle IGA (Score 0,1) observed difference.
As above.	Assuming a CCl dropout rate, CCl subjects receiving FMX103 and CCl subjects...	Assuming a CCl dropout rate, CCl subjects receiving FMX103 and CCl subjects...	Corrected for larger study sample size.
As above.	Therefore, the sample size needed to provide 90% power for both co-primary endpoints is CCl and CCl subjects...	Therefore, the sample size needed to provide at least 90% power for both co-primary endpoints is CCl and CCl subjects...	Corrected for larger study sample size.
Synopsis (Statistical Methods); Sect. 11.5.1 Primary Efficacy Endpoints	...treatment success is defined as a 2-step improvement...	...treatment success is defined as at least a 2-step improvement...	Clarification of treatment success criteria.
Synopsis (Number of Subjects (planned); Sect. 6 Study Population	...approximately 450 subjects...	...approximately 600 subjects...	Corrected for larger study sample size.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 7.2 Visit 1, Day 0/Baseline Visit	New text.	Dispense facial cleanser and moisturizer.	Clarification of the need to dispense cleanser and moisturizer at Day 0/Baseline.
Sect. 7.4	<ul style="list-style-type: none"> Confirm that subject continues to use only the provided facial cleanser. 	<ul style="list-style-type: none"> Confirm that subject continues to use only the provided facial cleanser and moisturizer. 	Reflecting the addition of moisturizer.
Sect. 7.5 and 7.6	<ul style="list-style-type: none"> Confirm that subject continues to use only the provided facial cleanser. 	<ul style="list-style-type: none"> Confirm that subject continues to use only the provided facial cleanser and moisturizer and dispense additional quantities as required. 	Clarification of cleanser and moisturizer re-supply to subjects.
Sect. 8.7 Prior/Concomitant Therapy	<ul style="list-style-type: none"> Subjects should use the facial cleanser <i>Cetaphil Gentle Skin Cleanser</i> (which will be provided by the Sponsor). An alternative, non-medicated cleanser may be used if agreed to by the Sponsor. 	<ul style="list-style-type: none"> As necessary, subjects should use the facial cleanser <i>Cetaphil Gentle Skin Cleanser</i> and the facial moisturizer <i>Eucerin Daily Protection Broad Spectrum SPF30 Face Lotion</i>. Both products will be provided by the Sponsor. Alternative non-medicated cleansers or moisturizers may be used if agreed to by the Sponsor. 	Addition of a SPF-containing moisturizer to support a positive skin care regimen during the study.
Synopsis, Endpoints and Outcomes;	The efficacy parameters will include inflammatory lesion counts, IGA at Day 0/Baseline and at Weeks 4, 8, and 12 (Final Visit), and the subject global assessment and satisfaction questionnaire at the Final Visit.	The co-primary efficacy parameters, include inflammatory lesion counts and IGA, will be evaluated at Day 0/Baseline and at Weeks 4, 8, and 12 (Final Visit). The Subject Global Assessment will be performed at Weeks 2, 4, 8, and 12 (Final Visit). The subject satisfaction questionnaire will be assessed at Week 12 (Final Visit) only.	Addition of more frequent subject global assessments to be conducted at each post-Day 0/Baseline visit.

Section(s)	Revision		Rationale
	Old Text	New Text	
Table 1 Schedule of Study Assessments and Procedures – Study FX2016-12: Subject Global Assessment	Subject Global Assessment at Week 12 (Final Visit) only	Additional Subject Global Assessments added at Weeks 2, 4, and 8.	Addition of more frequent subject global assessments to be conducted at each post-Day 0/Baseline visit.
Sect. 7.4; 7.5 and 7.6	New text.	Have the subject complete the Subject Global Assessment (Section 9.2.3)	As above.
Sect. 9.2.3	This score will be obtained from the subject at Visit 7 (Week 12/Final Visit) using the questionnaire in Appendix 1.	This score will be obtained from the subject at Visit 2 (Week 2), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12/Final Visit) using the questionnaire in Appendix 1.	As above.
Sect. 6.2 Exclusion Criteria 23	Screening electrocardiogram (ECG) that reveals a QTcF >500 msec.	Text removed.	A review of Solodyn [®] product labelling and an assessment of the safety and pharmacokinetics of minocycline when topically applied as FMX101 (4% minocycline HCl foam) to moderate-to-severe acne vulgaris subjects under maximum use conditions (4g per day for 21 days) warrants the removal of ECG assessments at Day 0/Baseline as it has been determined by the Sponsor as being an unnecessary procedure.
Table 1 Schedule of Study Assessments and Procedures – Study FX2016-12	Electrocardiogram	Text removed.	As above.
Sect. 7.1 Screening Visit	Perform 12-lead ECG (Section 10.7.1)	Text removed.	As above.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 10.7.1 Electrocardiograms	A standard 12-lead ECG will be performed at Screening only. Subjects will be supine and at rest for at least 10 minutes before measurement. Subjects will have their participation discontinued if an ECG reveals a QTcF>500msec (see Exclusion Criterion 23).	Text removed.	As above.
Global change	Visit schedule has been adjusted from Visit 1 (Day 0/Baseline); Visit 2 (Week 1); Visit 3 (Week 4); Visit 4 (Week 6); Visit 5 (Week 8); Visit 6 (Week 10) and Visit 7 (Week 12/Final Visit)	New schedule is Visit 1 (Day 0/Baseline); Early Follow-up (Week 1); Visit 2 (Week 2); Visit 3 (Week 4); Visit 4 (Week 8) and Visit 5 (Week 12/Final Visit).	To remove unnecessary study visits.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 7.3 Early Follow-up, Week 1 (±3 Days)	New text.	7.3 Early Follow-up, Week 1 (±3 Days) An early follow-up telephone call will be made 1 week after Visit 1, Day 0/Baseline. Record concomitant medications (Section 8.7). Record AEs (Section 10.8). Confirm that subject continues to use only the provided facial cleanser and moisturizer. Review application instructions to confirm that the subject continues to use the study drug as directed. Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.	To support early contact with subjects to address outstanding questions and reinforce study instructions.
Sect. 7.7 Visit 5, Week 12 (-3/+5 days) / Final Visit or Early Termination	Schedule/confirm a safety follow-up telephone call 4 weeks from Visit 7/Week 12 (Final Visit) date (±5 days) for subjects that will <u>not</u> participate in study FX2015-13 (Open label study) (Section 7.9).	Schedule/confirm a safety follow-up telephone call 4 weeks from Visit 5/Week 12 (Final Visit) date (±5 days) only for subjects that will not participate in study FX2015-13 (Open label study) (Section 7.9) and presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit).	Clarification of Safety Follow telephone call requirements.

Section(s)	Revision		Rationale
	Old Text	New Text	
Sect. 7.8 Safety Follow-Up (± 5 days)	A safety follow-up telephone call will be made 4 weeks after Visit 7/Week 12 (Final Visit) for <u>only</u> those subjects that do not participate in study FX2015-13 (Open label study). Follow up on existing and any new concomitant medications and adverse events will be recorded.	A safety follow-up telephone call will be made 4 weeks after Visit 5/Week 12 (Final Visit) for <u>only</u> those subjects that do not participate in study FX2015-13 (Open label study) and presented with either new or on-going adverse events at Visit 5/Week 12 (Final Visit). Follow up on these adverse events and any new concomitant medications will be recorded.	Clarification of AE reporting requirements.
Synopsis, Diagnosis and Main Criteria for Inclusion	At least 12 and not more than 50 inflammatory facial lesions (ie, papules/pustules),...	At least 15 and not more than 75 inflammatory facial lesions (ie, papules/pustules),...	Change inflammatory lesion count range in the inclusion criteria from 12-50 to 15-75.
Sect. 6.1 Inclusion Criteria	a. At least 12 and not more than 50 facial papules and pustules...	a. At least 15 and not more than 75 facial papules and pustules...	As above.
Table 2 Study Drug Kits and Treatments – Study FX2016-12	Additional kits of 2 canisters may be dispensed at other visits if required.	Text removed.	Redundant text due to change in visit schedule.
Sect. 8.1.1 Dosing Instructions	Additional kits will be available for dispensing at other visits (ie, Visits 4 and 6) to ensure enough product is available for daily dosing.	Text removed.	As above.
Sect. 12.2 Protocol Amendments	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	Text removed.	Misplaced text / repetition.

Section(s)	Revision		Rationale
	Old Text	New Text	
Appendix 3	New text.	Addition of investigator acknowledgement of protocol review and receipt.	Investigator confirmation of review and receipt of study protocol.

APPENDIX 1: Subject Global Assessment Questionnaire

Question: “Considering your rosacea just before starting treatment and considering your condition today, indicate the change you have experienced according to the scale below”:

- 5 = Much better than prior to treatment
- 4 = Slightly better than prior to treatment
- 3 = Same as prior to treatment
- 2 = Slightly worse than prior to treatment
- 1 = Much worse than prior to treatment

APPENDIX 2: Subject Satisfaction Questionnaire

The following 8 questions will be asked of the subject at Visit 5 (Week 12 / Final Visit):

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

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

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

The answer to Question 8 will be selected from the following:

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

APPENDIX 3: Acknowledgment Of Receipt And Review Of Protocol

Protocol Number: FX2016-12, Version 2

Protocol Title: A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (FX2016-12)

I hereby acknowledge receipt and review of the following Protocol:

1. Version 2, dated March 6th, 2017

Principal Investigator Name (Print)

Principal Investigator Signature

Date of Signature
(DD MMM YYYY)

CLINICAL PROTOCOL

Title Page

Study Title: A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (FX2016-12)

Sponsor: Foamix Pharmaceuticals, Inc.
520 US Highway 22, Suite 305
Bridgewater, NJ 08807

Protocol Identification: FX2016-12

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: 20 Jan 2017

Version of Protocol: 1

Supersedes: None

Prepared by: The Write Company, LLC

Confidentiality Statement

This document is the property of Foamix Pharmaceuticals, Inc., and is confidential and proprietary. The information contained herein is believed to be accurate and complete as of the date of preparation. The contents may not be used, divulged, published or otherwise disclosed without the expressed consent of Foamix Pharmaceuticals, Inc.

Signature Page

Title: A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (Study FX2016-12)

CONFIDENTIAL

Project Number: FMX103

Foamix Department	Name/Title	Signature	Date
CLINICAL DEVELOPMENT	PPD	PPD	
REGULATORY AFFAIRS	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:	A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Minocycline Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea (Study FX2016-12)	
Protocol No:	FX2016-12	
Study Centers:	Multicenter (approximately 30 sites in the USA)	
Publication (reference):	None	
Phase of Development:	3	
Objectives:	Primary Objectives: <ul style="list-style-type: none"> To determine the efficacy of FMX103 1.5% minocycline foam applied topically once daily for 12 weeks in the treatment of rosacea. To evaluate the safety of topical minocycline foam applied once daily for 12 weeks. 	
Study Design and Methods:	<p>This is a randomized, multicenter, double-blind, vehicle-controlled, 2-arm study to evaluate the safety and efficacy of FMX103 topical foam containing 1.5% minocycline compared to vehicle, in the treatment of subjects with moderate-to-severe facial papulopustular rosacea. Qualified subjects will be randomized in a 2:1 ratio (active:vehicle) to receive 1 of the following 2 treatments:</p> <ul style="list-style-type: none"> FMX103 minocycline foam 1.5% Vehicle foam <p>Subjects will be assigned to 1 of 2 treatments according to the randomization schedule. Subjects will apply (or have applied) the study drug topically once daily for 12 weeks as directed. Subjects will be advised to use the study drug at approximately the same time each day. Both the Investigator and subject will be blinded to the study drug identity.</p> <p>Subjects will return for visits at Weeks 1, 4, 6, 8, 10, and 12. Efficacy evaluations (inflammatory lesion counts and Investigator's Global Assessment [IGA] score) will be performed at Weeks 4, 8, and 12</p>	

	during the study.																		
Number of Subjects (planned):	The planned enrollment is approximately 450 male and female subjects. Subjects will be randomly assigned to the two treatment groups, FMX103 1.5% and vehicle, in a 2:1 ratio, respectively.																		
Diagnosis and Main Criteria for Inclusion:	<p>Healthy male or non-pregnant females, aged ≥18 years with a clinical diagnosis of moderate to severe facial papulopustular rosacea, defined as the presence of:</p> <ul style="list-style-type: none">• At least 12 and not more than 50 inflammatory facial lesions (ie, papules/pustules), and• An IGA of rosacea severity of moderate or severe using the following scale: <table><tr><th>Score</th><th>Grade</th><th>Description</th></tr><tr><td>0</td><td>Clear</td><td>No inflammatory papules or pustules</td></tr><tr><td>1</td><td>Almost clear</td><td>Few inflammatory papules or pustules</td></tr><tr><td>2</td><td>Mild</td><td>Several inflammatory papules or pustules</td></tr><tr><td>3</td><td>Moderate</td><td>Moderate number of inflammatory papules or pustules and no nodules</td></tr><tr><td>4</td><td>Severe</td><td>Many inflammatory papules or pustules, and up to 2 nodules</td></tr></table> <ul style="list-style-type: none">• Current or history of erythema and/or flushing <p>Subjects must be willing to minimize external factors that might trigger rosacea flare-ups (eg, spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, and alcoholic beverages).</p>	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
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																	
Test Product, Dose and Mode of Administration:	FMX103 minocycline foam 1.5%. Topical application, once daily to the face, for 12 weeks.																		
Reference Therapy:	Vehicle foam. Topical application, once daily to the face, for 12 weeks.																		
Study Duration:	Subject participation in the study will be up to 18 weeks: up to 6 weeks for Screening and Day 0/Baseline, and 12 weeks of study treatment. A safety follow-up telephone call will be conducted 4 weeks after completion of study treatment for <u>only</u> those subjects that do not participate in study FX2015-13 (Open label study).																		
Endpoints and Outcomes:	<p>Efficacy Evaluations</p> <p>The efficacy parameters will include inflammatory lesion counts, IGA at Day 0/Baseline and at Weeks 4, 8, and 12 (Final Visit), and the subject global assessment and satisfaction questionnaire at the Final Visit.</p> <p>Safety Evaluations</p> <p>The safety assessments will include adverse events (volunteered, observed, and elicited by general questioning in a non-suggestive manner), physical examinations, vital signs, clinical laboratory tests, and local signs and symptoms assessments (including erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis,</p>																		

	itching, peeling/desquamation, and hyperpigmentation) scores.
Statistical Methods:	<p>The primary population for efficacy analysis will be the intent-to-treat (ITT) population, using multiple imputations to impute missing values. Supportive efficacy analyses will be conducted on the per-protocol (PP) population, with no imputation for missing values.</p> <p>The co-primary efficacy endpoints will be the dichotomized IGA score where treatment success is defined as a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Week 12 compared to Day 0/Baseline and the absolute change in inflammatory lesion count at Week 12 compared to Day 0/Baseline.</p> <p>The key secondary endpoints will be analyzed hierarchically:</p> <ul style="list-style-type: none"> • Dichotomized IGA score where treatment success is defined as a 2-step improvement in score at Week 12 compared to Day 0/Baseline. • Percent change in inflammatory lesion count at Week 12 compared to Day 0/Baseline. <p>Continuous efficacy endpoints will be analyzed using analysis of covariance (ANCOVA). Dichotomized efficacy endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test.</p> <p>The tolerability and safety of topical minocycline foam applied daily for 12 weeks will be evaluated using summary statistics and individual subject data listings.</p> <p>The active treatment group will be tested against vehicle at the 0.05 two-sided level of significance. No statistical tests will be performed for any of the safety assessments.</p>

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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
BOCF	Baseline observation carried forward
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRO	Contract Research Organization
eCRF	Electronic case report form
ECG	Electrocardiogram
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 System
ITT	Intent-to-treat (population)
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model for repeated measures
OC	Observed cases
OTC	Over-the-counter
PP	Per-protocol (population)
PT	Preferred term
QTcF	QT interval corrected for heart rate using Fridericia's method
RBC	Red blood cell
RDC	Remote data capture
SAE	Serious adverse event
SAP	Statistical Analysis Plan
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
	Foamix Pharmaceuticals, Inc. 520 US Highway 22 Bridgewater, NJ 08807	Sponsor

External – Contract Research Organization (CRO)

Name	Affiliation / Address / Telephone Number	Responsibility
		

3 INTRODUCTION

Papulopustular rosacea is a chronic disorder affecting both the skin and the eye. 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.

Foamix has developed a topical minocycline foam product that is being evaluated for safety and efficacy in the treatment of rosacea. Minocycline hydrochloride is an established broad spectrum antibiotic that is used orally in the treatment of 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 has been evaluated in a Phase 2 study at two minocycline concentrations, 1.5% and 3%. The study included 232 subjects (males/females, aged ≥ 18 years) with moderate-to-severe papulopustular rosacea defined by the Investigator's Global Assessment (IGA) score and with ≥ 12 inflammatory facial lesions (papules/pustules) at Day 0/Baseline. Subjects were treated with FMX103 1.5%, FMX103 3%, or vehicle foam, once daily for 12 weeks. Efficacy and safety were evaluated at Weeks 2, 4, 8, and 12, with an additional safety follow-up visit at Week 16. The primary efficacy end point was the absolute change in inflammatory lesion count at Week 12. Other assessments included IGA improvement of ≥ 2 grades and reaching an IGA score of "clear" or "almost clear" (IGA 0/1), clinical assessment of erythema, and safety and tolerability.

At Week 12, both the 1.5% and 3% doses of FMX103 significantly reduced the number of papules and pustules vs. vehicle (both $p < 0.001$, intent-to-treat [ITT] population). The mean reduction in lesion count from Day 0/Baseline was 21.1 for the FMX103 1.5% dose, 19.9 for the FMX103 3% dose, and 7.8 for the vehicle. The corresponding percent reductions were 61.4% and 55.5% for the 1.5% and 3% doses, respectively, and 29.7% for the vehicle.

Both the 1.5% and 3% doses of FMX103 were statistically significantly better than vehicle in improving IGA scores by ≥ 2 grades at week 12 ($p = 0.002$ and $p = 0.032$, respectively). Both doses were also statistically significantly better than vehicle in achieving an IGA of "clear or almost clear" (score 0/1) at Week 12 ($p = 0.001$ and $p = 0.041$, respectively). Both FMX103 1.5% and 3% doses appeared to be generally safe and well-tolerated. Treatment-related dermal reactions were reported in 1 subject from the FMX103 1.5% dose group (considered mild) and in a few subjects

from the FMX103 3% dose group (mild, n=1; moderate, n=2; severe, n=1). No treatment-related systemic adverse events (AEs) were reported and discontinuation due to AEs (eczema, n=1; rosacea, n=1; burning sensation, n=1) was reported in 3 subjects in the FMX103 3% dose group.

As a consequence of the above, the FMX103 1.5% dose concentration has been selected for further development. This Phase 3 study will further assess the safety and efficacy of topical minocycline HCl foam, 1.5%, applied once daily compared with vehicle foam for the treatment of moderate-to-severe papulopustular rosacea.

4 STUDY OBJECTIVES

The primary objectives of the study are:

- To determine the efficacy of FMX103 1.5% minocycline foam applied topically once daily for 12 weeks in the treatment of rosacea.
- To evaluate the tolerability and safety of topical minocycline foam applied once daily for 12 weeks.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is a randomized, multicenter, double-blind, vehicle-controlled, 2-arm study to evaluate the safety and efficacy of FMX103 topical foam containing 1.5% minocycline compared to vehicle, in the treatment of subjects with moderate-to-severe facial papulopustular acne rosacea.

Qualified subjects will be randomized in a 2:1 ratio (active:vehicle) to use once daily one of the following two treatments:

- FMX103 minocycline foam 1.5%
- Vehicle foam

Subjects will be assigned to 1 of 2 treatments according to the randomization schedule. Subjects will apply (or have applied) the study drug topically once daily for 12 weeks as directed. Subjects will be advised to use the study drug at approximately the same time each day, preferably in the evening about 1 hour before bedtime. Both the Investigator and subject will be blinded to the study drug identity.

Subjects will return for visits at Weeks 1, 4, 6, 8, 10, and 12. Efficacy evaluations (inflammatory lesion counts [Section 9.1.1] and IGA score [Section 9.1.2]) will be performed at Weeks 4, 8, and 12 during the study. Other assessments will be performed as described in Section 9 and Section 10.

5.2 Rationale for Study Design and Dose Selection

A randomized, multicenter, double-blind, vehicle-controlled study design has been selected in order to assess the efficacy of the study drug. The subjects will be selected according to predefined entry criteria. The study treatment duration of 12 weeks is expected to be sufficient to show a treatment effect.

The concentration of minocycline in the composition was selected according to formulation integrity and stability considerations and based on the results of Phase 2 Study FX2015-10 (described above in [Section 3](#)).

Because of the mode of action of tetracycline drugs, the primary efficacy endpoints will be the effect on inflammatory lesion counts and IGA scores ([Section 9](#)).

6 STUDY POPULATION

The study will randomize approximately 450 subjects to active or vehicle treatment (in a 2:1 ratio) at approximately 30 sites in the US.

6.1 Inclusion Criteria

Subjects were included in the study if they met all of the following inclusion criteria at the time of enrollment:

1. Male or female ≥ 18 years-of-age.
2. Moderate-to-severe rosacea (as per the IGA score; [Table 3](#)) on the proposed facial treatment area consisting of:
 - a. At least 12 and not more than 50 facial papules and pustules, excluding lesions involving the eyes and scalp;
 - b. No more than 2 nodules on the face.
3. Presence of or history of erythema and/or flushing on the face.
4. If a female 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.
5. Willing to minimize external factors that might trigger rosacea flare-ups (eg, spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds, and alcoholic beverages).
6. Subjects who use make-up must have used the same brands/types of make-up for a minimum period of 14 days prior to study entry and must agree to use the same make-up, brand/type, or frequency of use, throughout the study.
7. Completed and signed an appropriately administered Informed Consent Form (ICF) prior to any study-related procedures.

6.2 Exclusion Criteria

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

1. Woman who is pregnant, lactating, or planning to become pregnant during the study period.
2. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea.

3. Moderate or severe rhinophyma, dense telangiectasia (score 3, severe; [Section 10.7.2.2](#)), or plaque-like facial edema.
4. An active nodule on the face >5 mm in diameter.
5. Excessive facial hair (eg, beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.
6. History of hypersensitivity or allergy to minocycline, any other tetracycline, or of any other component of the formulation.
7. Severe erythema, dryness, scaling, pruritus, stinging/burning, or edema.
8. Active ocular rosacea (eg, conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics.
9. Use within 6 months prior to Day 0/Baseline of oral retinoids (eg, Accutane[®]) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
10. Initiation of use of estrogens or oral contraceptives less than 3 months prior to Day 0/Baseline.
11. Use within 1 month prior to Day 0/Baseline of:
 - a. Topical retinoids to the face.
 - b. Systemic antibiotics known to have an impact on the severity of facial rosacea (eg, containing tetracycline and its derivatives, erythromycin and its derivatives, sulfamethoxazole, or trimethoprim). Subjects requiring systemic antibiotics not known to affect rosacea will be considered on a case-by-case basis.
 - c. Systemic corticosteroids (Note: intranasal and inhalational corticosteroids do not require a washout and maybe used throughout the trial if the subject is on a stable dose).
12. Use within 2 weeks prior to Day 0/Baseline of:
 - a. Topical corticosteroids.
 - b. Topical antibiotics.
 - c. Topical medications for rosacea (eg, metronidazole).
13. Use of a sauna during the 2 weeks prior to Day 0/Baseline and during the study.
14. Had wax epilation of the face within 2 weeks prior to Day 0/Baseline.
15. Active bacterial folliculitis.
16. Consumption of excessive alcohol, abuse of licit or illicit drugs, or a condition that, in the opinion of the Investigator, could compromise the subject's ability to comply with study requirements.
17. Participation in activities that involve excessive or prolonged exposure to sunlight or weather extremes, such as wind or cold.

18. Presence of any clinically significant condition or situation, other than the condition being studied, that in the opinion of the Investigator would interfere with the study evaluations or optimal participation in the study.
19. Participation in an investigational drug study (ie, subject has been treated with an investigational drug) within 30 days prior to Day 0/Baseline. Subjects who are participating in non-treatment studies such as observational studies or registry studies can be considered for inclusion.
20. Previously enrolled in this study.
21. Prior laser therapy (for telangiectasia or other conditions), electrodesiccation, or phototherapy (eg, ClearLight[®]) to the facial area within 180 days prior to Day 0/Baseline.
22. Prior cosmetic procedures (eg, facials) that may affect the efficacy and safety profile of the investigational product within 14 days prior to Day 0/Baseline.
23. Screening electrocardiogram (ECG) that reveals a QTcF >500 msec.

7 STUDY PROCEDURES

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

The eligible subject who is willing to participate in the study will then sign an appropriately administered ICF prior to any study-related procedures being performed.

Procedures at the Screening Visit will include obtaining blood and urine samples for clinical laboratory tests. The results of these tests must be no more than 45 days old at the time of the Day 0/Baseline Visit and randomization.

If a subject who has agreed to participate in the study and signed the ICF is currently undergoing rosacea therapy identified in Exclusion Criteria 11 and 12, they must first enter a washout period (ie, 1 month or 2 weeks, as specified in Exclusion Criteria 11 and 12, respectively) before beginning the screening procedures.

The schedule of study assessments and procedures and the time point at which they will be performed during the study is presented in Table 1. If a subject prematurely withdraws from the study, the subject should return to the study site for an early termination visit during which all evaluations described under Final Visit 7/Week 12 must be performed.

Table 1 Schedule of Study Assessments and Procedures – Study FX2016-12

Assessment or Procedure	Screening	Day 0 / Baseline ^a	Visits						Final Visit ^b	Safety Follow-up ^g
Visit		1	2	3	4	5	6	7		
Week			1	4	6	8	10	12		
Informed consent	X									
Demographic data	X									
Assign subject identification	X									
Medical/surgical/medication history	X									
Inclusion/exclusion criteria	X	X								
Physical examination, height, weight ^c		X						X		
Electrocardiogram	X									
Blood pressure/heart rate ^d		X	X	X	X	X	X	X		
Blood and urine samples for clinical laboratory tests	X							X		
Urine pregnancy test (females of childbearing potential only)	X	X		X		X		X		
Lesion counts	X	X		X		X		X		
Investigator's Global Assessment	X	X		X		X		X		
Subject Global Assessment								X		
Subject Satisfaction Questionnaire								X		
Local signs and symptoms assessments ^e	X	X	X	X	X	X	X	X		
Photography		X		X		X		X		
Randomization		X								
Concomitant medications		X	X	X	X	X	X	X		X
Adverse events		X	X	X	X	X	X	X		X
Perform drug accountability				X		X		X		
Collect used drug canister(s)				X	X	X	X	X		
Dispense study drug		X	X	X	X ^f	X	X ^f			
Schedule/confirm next visit	X	X	X	X	X	X	X			

- Day 0/Baseline must occur within 45 days of Screening. Blood test results must not show clinically significant abnormalities.
- If a subject prematurely withdraws from the study, all evaluations described under Visit 7/Week 12 (Final Visit) must be performed at an Early Termination Visit.
- Height to be measured only at Day 0/Baseline.
- Measure blood pressure and heart rate after the subject has been sitting for at least 5 minutes at rest.
- 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.
- Dispense one kit (2 canisters) of study drug only if necessary at Visits 4 and 6.
- A safety follow-up telephone call will be made 4 weeks after Visit 7/Week 12 (Final Visit) for only those subjects that do not participate in study FX2015-13 (Open label study).

7.1 Screening Visit

- Obtain a signed and dated, written ICF prior to any study-related procedures.
- Obtain demographic data.
- Using the Interactive Response Technology System (IRT), assign the subject an identification number.
- Obtain medical/surgical history ([Section 10.1](#)).
- Obtain history of prior medication usage (including previous use of rosacea medications); record start and stop dates of any medications used in the last 3 months ([Section 10.2](#)).
- Assess eligibility according to the inclusion ([Section 6.1](#)) and exclusion criteria ([Section 6.2](#)).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test ([Section 10.6.1](#)).
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory ([Section 10.6.2](#)).
- Perform 12-lead ECG ([Section 10.7.1](#)).
- Perform facial lesion count of inflammatory lesions ([Section 9.1.1](#)).
- Perform IGA ([Section 9.1.2](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Schedule/confirm the next study visit.

7.2 Visit 1, Day 0/Baseline Visit

- Confirm eligibility according to the inclusion ([Section 6.1](#)) and exclusion criteria ([Section 6.2](#)).
- Perform physical examination including height and weight ([Section 10.5](#)).
- Measure blood pressure and heart rate ([Section 10.4](#)).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test ([Section 10.6.1](#)).
- Perform facial lesion count of inflammatory lesions ([Section 9.1.1](#)).
- Perform IGA ([Section 9.1.2](#)).
- Perform photography ([Section 9.3](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Randomize the subject using the IRT when all criteria have been met.
- Record concomitant medications ([Section 8.7](#)).

- Record AEs ([Section 10.8](#)).
- Dispense one kit (2 canisters) of study drug.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.3 Visit 2, Week 1 (±3 Days)

- Measure blood pressure and heart rate ([Section 10.4](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Confirm that subject continues to use only the provided facial cleanser.
- Collect used study canister (if applicable).
- Dispense one kit (2 canisters) of study drug.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.4 Visit 3, Week 4 (±3 Days)

- Measure blood pressure and heart rate ([Section 10.4](#)).
- Perform facial lesion count of inflammatory lesions ([Section 9.1.1](#)).
- Perform IGA ([Section 9.1.2](#)).
- Perform photography ([Section 9.3](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test ([Section 10.6.1](#)).
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Perform drug accountability to assess compliance ([Section 8.2](#)).
- Collect used study drug canister (if applicable).
- Dispense one kit (2 canisters) of study drug.
- Confirm that subject continues to use only the provided facial cleanser.

- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.5 Visit 4, Week 6 (±3 Days)

- Measure blood pressure and heart rate ([Section 10.4](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Collect used study drug canister (if applicable).
- Dispense one kit (2 canisters) of study drug (if necessary).
- Confirm that subject continues to use only the provided facial cleanser.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.6 Visit 5, Week 8 (±3 Days)

- Measure blood pressure and heart rate ([Section 10.4](#)).
- Perform facial lesion count of inflammatory lesions ([Section 9.1.1](#)).
- Perform IGA ([Section 9.1.2](#)).
- Perform photography ([Section 9.3](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test ([Section 10.6.1](#)).
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Perform drug accountability to assess compliance ([Section 8.2](#)).
- Collect used study canister (if applicable).
- Dispense one kit (2 canisters) of study drug.
- Confirm that subject continues to use only the provided facial cleanser.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.7 Visit 6, Week 10 (± 3 Days)

- Measure blood pressure and heart rate ([Section 10.4](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Collect used study drug canister (if applicable).
- Dispense one kit (2 canisters) of study drug (if necessary).
- Confirm that subject continues to use only the provided facial cleanser.
- Schedule/confirm the next study visit and remind subject to avoid overexposure to sunlight and to use the same make-up brand/type, or frequency of use, throughout the study as applicable.

7.8 Visit 7, Week 12 ($-3/+5$ days)/ Final or Early Termination

- Perform physical examination including weight ([Section 10.5](#)).
- Measure blood pressure and heart rate ([Section 10.4](#)).
- Collect blood and urine samples for clinical laboratory tests and send to the central laboratory ([Section 10.6.2](#)).
- Collect a urine sample from female subjects of childbearing potential for a urine pregnancy test ([Section 10.6.1](#)).
- Perform facial lesion count of inflammatory lesions ([Section 9.1.1](#)).
- Perform IGA ([Section 9.1.2](#)).
- Perform photography ([Section 9.3](#)).
- Perform local signs and symptoms assessments ([Section 10.7.2](#)).
- Have the subject complete the Subject Global Assessment ([Section 9.2.3](#)).
- Have the subject complete the Subject Satisfaction Questionnaire ([Section 9.2.4](#)).
- Record concomitant medications ([Section 8.7](#)).
- Record AEs ([Section 10.8](#)).
- Collect all used and full study drug canisters.
- Perform drug accountability to assess compliance and record the date of the last dose ([Section 8.2](#)).
- Schedule/confirm a safety follow-up telephone call 4 weeks from Visit 7/Week 12 (Final Visit) date (± 5 days) for subjects that will not participate in study FX2015-13 (Open label study) ([Section 7.9](#)).

7.9 Safety Follow-Up (±5 days)

A safety follow-up telephone call will be made 4 weeks after Visit 7/Week 12 (Final Visit) for only those subjects that do not participate in study FX2015-13 (Open label study). Follow up on existing and any new concomitant medications and adverse events will be recorded.

8 STUDY TREATMENTS

This study will include FMX103 minocycline foam 1.5% and vehicle foam.

8.1 Treatments Administered

The description of study drug kits and treatments is shown below in [Table 2](#).

Table 2 Study Drug Kits and Treatments – Study FX2016-12

Dosage form description:	Foam containing minocycline HCl 1.5% or vehicle foam
Package description:	Canisters, each containing 25 g of the clinical trial supply foam
Daily dose:	Once daily 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) or 0.0 mg (vehicle) of minocycline.
Cumulative maximal dose for dosing (12 weeks):	630 mg (1.5%) minocycline
Dispensing:	Kits consisting of 2 canisters, each canister containing 25 g of FMX103 minocycline formulation, 1.5%, or vehicle dispensed at Visit 1 (Day 0/Baseline), Visit 2 (Week 1), Visit 3 (Week 4), and Visit 5 (Week 8). Additional kits of 2 canisters may be dispensed at other visits if required.

8.1.1 Dosing Instructions

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

Study drug kits containing 2 canisters of investigational drug will be dispensed at Visit 1 (Day 0/Baseline), Visit 2 (Week 1), Visit 3 (Week 4), and Visit 5 (Week 8). Additional kits will be available for dispensing at other visits (ie, Visits 4 and 6) to ensure enough product is available for daily dosing.

After shaking the canister well, a small amount of study drug (about ½ gram or a cherry-sized amount) should be expressed from the canister onto the finger tips and then applied as a thin layer over all involved areas of the face. Additional drug may be used as needed to assure the entire involved area is treated.

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

8.1.2 Manufacturer

The manufacturer of the investigational product is ASM Aerosol-Service AG, Moehlin, Switzerland.

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% and vehicle canisters must be stored at 2°C – 8°C until being dispensed to the subject. Subsequently, they must be stored at 20°C – 25°C (refer to USP Controlled Room Temperature). 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 use of the study drug. The Investigator or designee will verify the contents of the drug shipment and confirm receipt of the study drug in the 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 bottles of study drug will be returned to the Sponsor or designee by the time of the site's close-out visit. Receipt, distribution, and return of the study drug must be properly documented on forms provided by the Sponsor or designee.

8.4 Method of Assignment of Study Drug

After pretreatment clinical evaluations and all other Screening procedures have been completed, authorized site personnel will acknowledge that the applicable subject met all the specified inclusion criteria ([Section 6.1](#)) and none of the exclusion criteria ([Section 6.2](#)). Assignment to a treatment group will then follow a predetermined list of randomization numbers, with each successive number receiving 1 of the 2 treatments in random order. Authorized site personnel will use the IRT system to assign a kit number that corresponds to the randomization schedule. The kit box with the assigned kit number will be dispensed to the subject.

The randomization code will be provided by Premier Research, Research Triangle Park, NC.

8.5 Selection and Timing of Doses in the Study

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

8.6 Blinding

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

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

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

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

If unblinding is necessary, the subject will be withdrawn from the study and Early Termination Visit (ie, Visit 7 [Week 12]) assessments will be completed.

8.7 Prior/Concomitant Therapy

Subjects should use the facial cleanser *Cetaphil Gentle Skin Cleanser* (which will be provided by the Sponsor). An alternative, non-medicated cleanser may be used if agreed to by the Sponsor.

The use of or change in the dose of any and all concomitant 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. Therapies (medication and non-medication therapies) not restricted by the protocol may be used. Non-prohibited chronic therapies being used at Day 0/Baseline may be continued. If a female subject is using an oral contraceptive product, she should have been on the same product for at least 3 months and she should continue using the same or equivalent product for the duration of the study.

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

All topical or systemic medications listed in the exclusion criteria are prohibited during this study. Similarly, no other topical medications are permitted to be used on the face during this period.

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 is not postmenopausal (defined as amenorrhea >12 consecutive months). Females of childbearing potential must have a negative urine pregnancy test and, if they are sexually active or become sexually active during the study, must use an effective method of birth control such as those listed below during the course of the study. The following is not an all-inclusive list; the subject must discuss with the Investigator the most appropriate form of birth control:

- Hormonal methods
 - Oral contraceptives – (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 kits (empty/used/unused) at the appropriate visits. The study site personnel will question the subject on the history of study drug use since the last visit. A subject who deviates significantly from the prescribed dosage will be counseled.

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 Co-Primary Efficacy Assessments

The co-primary efficacy assessments will include the inflammatory lesion counts and the IGA of severity of disease. Lesion counts, IGA, and other efficacy evaluations 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 will be performed at Screening and Visit 1 (Day 0/Baseline) to confirm eligibility, and again at Visit 3 (Week 4), Visit 5 (Week 8), and Visit 7 (Week 12/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 will be performed at Screening and Visit 1 (Day 0/Baseline) to confirm eligibility, and again at Visit 3 (Week 4), Visit 5 (Week 8), and Visit 7 (Week 12/Final Visit).

Table 3 IGA Scale for Rosacea – Study FX2016-12

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 CCl Efficacy Assessments

9.2.1 Percent Change in Inflammatory Lesion Counts

The percent change in inflammatory lesion counts at Visit 7 (Week 12/Final Visit) compared to Visit 1 (Day 0/Baseline) will be evaluated.

9.2.2 Interim Change in Inflammatory Lesion Counts

The absolute CCl change in inflammatory lesion counts at Visit 3 (Week 4) and Visit 5 (Week 8) compared to Visit 1 (Day 0/Baseline) will be evaluated.

9.2.3 Subject Global Assessment

This score will be obtained from the subject at Visit 7 (Week 12/Final Visit) using the questionnaire in [Appendix 1](#).

9.2.4 Subject Satisfaction Questionnaire

A subject satisfaction questionnaire ([Appendix 2](#)) will be administered at Visit 7 (Week 12/Final Visit).

9.3 Photography

Photography of the full face will be performed at Day 0/Baseline and at Weeks 4, 8, and 12 using recognized methods. The equipment and techniques for this photography and for archiving the images are described in the Study Manual. Photographs will be reviewed at the site and by the sponsor for quality. Photographs will not be used to assess the lesion counts or the IGA, but will be archived to be available for subsequent review, if required, by the sponsor, auditors, or the FDA.

10 SAFETY ASSESSMENTS

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

10.1 Medical/Surgical History

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

10.2 Medication History

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

10.3 Concomitant Medications

All topical or systemic medications listed in the exclusion criteria are prohibited. No other topical medications are permitted to be used on the face. All medication that the subject is currently taking or any change in medication or dosage since the last visit will be documented throughout the study. The use of or change in the dose of any and all concomitant medication, either prescription or 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.

10.4 Vital Signs

Heart rate and blood pressure (BP) will be measured at all post-Day 0/Baseline 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.

10.5 Physical Examination

A complete physical examination (excluding the genitourinary examination) will be performed.

Weight will be recorded at the Visit 1 (Day 0/Baseline) and Visit 7 (Week 12/Final Visit). Height will be measured at Visit 1 (Day 0/Baseline) only.

10.6 Clinical Laboratory Tests

Serum chemistry, hematology and urinalysis will be evaluated at the Screening Visit and Visit 7 (Week 12/Final Visit). All clinical laboratory tests will be performed at 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 FX2016-12

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

10.6.1 Urine Pregnancy Test

A urine pregnancy test will be performed on all females of childbearing potential at the Screening Visit, Visit 1 (Day 0/Baseline), Visit 3 (Week 4), Visit 5 (Week 8), and Visit 7 (Week 12/Final Visit) or when a subject prematurely withdraws from the study.

10.6.2 Sample Collection, Storage, and Shipping

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

10.7 Other Safety Measurements

10.7.1 Electrocardiograms

A standard 12-lead ECG will be performed at Screening only. Subjects will be supine and at rest for at least 10 minutes before measurement. Subjects will have their participation discontinued if an ECG reveals a QTcF >500 msec (see Exclusion Criterion [23](#)).

10.7.2 Local Signs and Symptoms Assessments

The severity of each of the following local signs and symptoms will be measured at Screening, Visit 1 (Day 0/Baseline), and at each study visit: 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 medication or is the reason for discontinuation from the study.

10.7.2.1 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

10.7.2.2 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

10.7.2.3 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

10.7.2.4 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

10.7.2.5 Dryness/Xerosis

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

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

10.7.2.6 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

10.7.2.7 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

10.7.2.8 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

10.8 Adverse Events

10.8.1 Method of Determining Adverse Events

Safety assessments will include recording AEs reported spontaneously by the subject or observed by the Investigator. AEs will be recorded at each visit on the appropriate CRF. Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded 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 10.8.4](#)) and recorded in the subject's source documents, and the results will be provided to the Sponsor.

For AE definitions and reporting requirements, refer to [Section 10.8.2](#) and [Section 10.8.3](#), respectively.

10.8.2 Adverse Event Definitions

10.8.2.1 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.

10.8.2.2 Serious Adverse Events

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

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

10.8.2.3 Severity of Adverse Events

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

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

10.8.2.4 Relationship of Adverse Events to Study Treatments

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

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

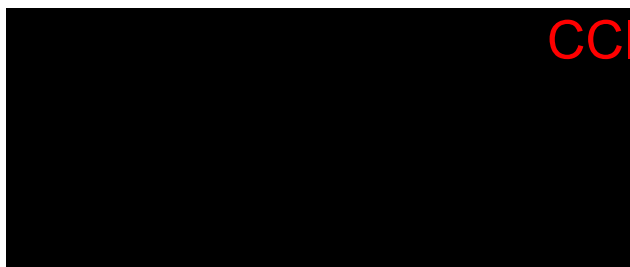
10.8.2.5 Adverse Events Expectedness

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.

10.8.3 Reporting Adverse Events

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

Any SAEs occurring in a subject receiving study drug must be reported to the Sponsor or designee within 24 hours of the site being informed of the event, even if the event does not appear to be drug-related. The report must be done by faxing the completed SAE Report Form to the Sponsor or designee. Any pertinent follow-up information should be provided in a similar manner. Contact information is provided below:



10.8.4 Adverse Event Follow-up

Adverse events that are ongoing when a subject withdraws from or completes the study will be followed until resolution or stabilization (in the opinion of the Investigator), or for 30 days,

whichever is shorter. Investigators and the Sponsor will decide if longer follow-up is appropriate on a case-by-case basis. Subjects who experience any clinically significant AE will remain under medical supervision until the Investigator or the Sponsor's medical monitor deems the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up.

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

10.8.4.1 Pregnancy Reporting

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

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

A urine pregnancy test will be performed on all females of childbearing potential as described in [Section 10.6.1](#).

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, missed or late menstrual period). If a subject or Investigator suspects that the subject may be pregnant at any time before or during the study, the study drug must be withheld until the results of laboratory pregnancy testing are available. The Sponsor and site monitor must be notified and 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.

10.8.5 Clinically Significantly Abnormal Laboratory Results

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

10.9 Appropriateness of Safety Measurement

The safety assessments to be utilized 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 (SAP) will be finalized prior to breaking of the study blind.

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

11.2 Determination of Sample Size

In the Phase 2 Study FX2015-10, the proportion of subjects with an IGA score of 0 or 1 after [REDACTED] of treatment was [REDACTED] in the FMX103 1.5% dose group compared to [REDACTED] for the vehicle dose group. Table 5 provides alternate assumptions on this primary response criterion with corresponding implications on sample size. Power was set to 90% and a type-1 error was set to a two-sided test with a 0.05 level of significance. Sample size was calculated based on Fisher's Exact test.

Table 5 Sample Size Calculations Based on IGA Scores after [REDACTED] of Treatment in Phase 2 Study FX2015-10

Vehicle IGA (Score 0,1)	FMX103 1.5% IGA (Score 0,1)	Sample Size (Vehicle, Active)
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Assuming a [REDACTED] dropout rate, 300 subjects receiving FMX103 and 150 subjects receiving vehicle will provide at least 90% power for a statistically significant difference on an IGA score of 0 or 1.

For the co-primary endpoint of change from Day 0/Baseline to [REDACTED] in inflammatory lesion count, in the Phase 2 study the FMX103 1.5% dose group had a mean reduction of [REDACTED] lesions whereas the vehicle had a mean reduction of [REDACTED] lesions. The standard deviation was [REDACTED]. For a 90% power, [REDACTED] and [REDACTED] subjects in the FMX103 1.5% and vehicle groups, respectively, will be needed. Therefore, the sample size needed to provide 90% power for both co-primary endpoints is [REDACTED] and [REDACTED] subjects in the FMX103 1.5% and vehicle groups, respectively.

11.3 Analysis Populations

The following populations will be defined for analysis:

- Intent-to-Treat (ITT) population: all randomized subjects.
- Per-Protocol (PP) population: defined as the subset of the ITT population without any protocol deviations that may have an impact on the efficacy assessments. Subjects to be included in the PP population will be determined by the Sponsor/CRO prior to the unblinding of the study.

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

- Failure to meet inclusion/exclusion criteria
- Have administered any interfering concomitant medications
- Have not, in the opinion of the Investigator, been compliant with the treatment regimen (eg, reported frequent missed doses)
- Randomization error

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

- **Safety Population:** all randomized subjects who use any study product. Subjects who have no post-Day 0/Baseline assessments will be included in the Safety population unless all dispensed study drug is returned unused.

The ITT population will be the primary population for efficacy analysis. The PP population will be secondary for the co-primary endpoints only. The Safety population will be used for the analyses of safety endpoints.

All efficacy analyses will be conducted according to the randomized treatment assignment; all safety analyses will be conducted according to the treatment actually received.

11.4 Subject Accounting, Demographics, and Day 0/Baseline Characteristics

Demographics, Day 0/Baseline characteristics, and prior and concomitant medications will be summarized by treatment. Study completion status and reasons for discontinuation will also be displayed by treatment.

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

11.5 Efficacy Endpoints

The primary population for all efficacy analyses will be the ITT population. For the analyses of the co-primary and secondary efficacy endpoints based on the ITT population, a variety of methods will be used to impute missing data, including multiple imputation (MI), last-observation-carried forward (LOCF), and Day 0/Baseline observation carried forward (BOCF). MI will be the primary imputation method. Sensitivity analyses using LOCF and BOCF will be performed only on the co-primary efficacy endpoints to assess the robustness of alternate imputation assumptions. For the continuous efficacy measure, a mixed effects model for repeated measures (MMRM) analysis will also be conducted as a sensitivity analysis. All supportive analyses using the PP population will use the Observed-Cases (OC) approach, that is there will be no imputation for missing data at any time point. No other imputations will be made unless otherwise specified.

For all efficacy analyses, subjects will be analyzed according to the treatment group to which they were randomized.

11.5.1 Primary Efficacy Endpoints

The co-primary efficacy endpoints are:

- The absolute change in the inflammatory lesion count at Week 12 compared to Day 0/Baseline.
- The dichotomized IGA score where treatment success is defined as a 2-step improvement resulting in a 0 (clear) or 1 (almost clear) score at Week 12 compared to Day 0/Baseline.

The null hypothesis of the equality of the FMX103 1.5% and vehicle means for absolute change from Day 0/Baseline to Week 12 in the inflammatory lesion count and the equality of IGA success rates at Week 12 will each be tested at a two-sided 0.05 level of significance. Change from Day 0/Baseline in inflammatory lesion count will be analyzed using an analysis of covariance (ANCOVA), with treatment as a main effect, Day 0/Baseline inflammatory lesion count as a covariate, and investigational site as a blocking factor. Investigational site-by-treatment interaction will be tested at a two-sided 0.1 level, and if significant, will be further explored. The dichotomized IGA will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, stratified by investigational site.

11.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The dichotomized IGA score where success is defined as a 2-step improvement in score at Week 12 compared to Day 0/Baseline.
- The percent change in inflammatory lesion count at Week 12 compared to Day 0/Baseline.
- The absolute change from Day 0/Baseline in the inflammatory lesion count and IGA treatment success at the interim visit at Week 8.
- The absolute change from Day 0/Baseline in the inflammatory lesion count and IGA treatment success at the interim visit at Week 4.

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

11.5.3 [REDACTED] CCI

[REDACTED] CCI

- [REDACTED] CCI
- [REDACTED] CCI

11.6 Safety Endpoints

Safety endpoints will be reported on the Safety population. Subjects will be reported according to the treatment they actually received. Safety assessment will be based on descriptive statistics

and individual 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 pre-treatment, or worsen relative to the pre-treatment state. Summaries of AEs will be limited to TEAEs. The number and percentage of subjects reporting events under each System Organ Class (SOC) and preferred term (PT) will be summarized for each treatment group. At each level of summarization, a subject will be counted only once if he/she reported one or more events. The severity of TEAEs and relationship to study drug will be summarized in a similar manner. For summaries of relationship to study drug, a subject will be classified according to the closest relationship. For summaries of TEAE severity, a subject will be classified according to the highest severity.

TEAEs, vital signs, and clinical laboratory measurements will be summarized by treatment group using descriptive statistics. For vital signs, change from Day 0/Baseline values will also be summarized. For all safety variables, subject data listings will be provided.

Local signs and symptoms 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 10.7.2](#).

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 prematurely withdraw from the study 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 Day 0/Baseline and at each post-Day 0/Baseline time point. Changes from Day 0/Baseline will also be summarized. Day 0/Baseline is defined as the last non-missing value prior to the first dose of study drug.

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 Day 0/Baseline with the number of subjects with low, normal, or high values at the Final Visit. Day 0/Baseline is defined as the last non-missing value prior to the first dose of study drug.

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

11.7 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 immediately notify the Sponsor of any regulatory authority inspections. The Investigator will be informed about the outcome of any Sponsor audit.

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

Monitoring visits will take place on a regular basis according to the enrollment rate and number of subjects enrolled at each investigational site. During these visits, the monitor will check the completion of the CRF entries, compliance with the study protocol and with GCP-ICH, and their agreement with the source data. The monitor will also verify the correct use of the study drug. At a 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.

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.

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 the IRB's guidelines.

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

12.4 Withdrawal of Subjects

Withdrawn subjects are those who do not complete all evaluations and procedures outlined in the protocol. Subjects who discontinue taking study drug for any reason must also be withdrawn from the study. Subjects may be withdrawn from the study because of 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 10.8.4](#).
- **Abnormal Laboratory Result:** Any clinically significant laboratory abnormality that requires withdrawal of the subject from the study should be considered an AE leading to withdrawal. If possible, laboratory tests will be repeated for any results that were clinically significantly abnormal until the abnormality is resolved or stabilized to the satisfaction of the Investigator in consultation with the medical monitor.
- **Lost to Follow-up:** Confirmed at minimum by two phone calls and a traceable letter without answer.
- **Subject Request:** Subject requests, for any reason (eg, AE), to be withdrawn or withdraws his/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, relocation of subject, etc. If a subject becomes pregnant during the study, the subject will be withdrawn from the study and followed through conclusion of the pregnancy.

If a subject is withdrawn from the study following the start of study drug, all Visit 7 (Week 12/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, which will make reasonable efforts to assure that the results are published in a peer-reviewed journal. As some of the information concerning the investigational product and development activities at the Sponsor may be of a strictly confidential 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 (IRB)

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/her entry into the study (ie, before examinations and procedures associated with selection for the study are initiated). Each subject will have ample opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Following this informative discussion, the subject will be asked if he/she is willing to sign a statement of informed consent. Only subjects who voluntarily sign the ICF may enter the study.

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

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

13.6 Financing

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

Completion of Financial Disclosure Forms will be required before the study starts. Any additions to the primary site personnel will necessitate the completion of new Financial Disclosure Forms. This information will also be collected at site closure and 1 year after the completion of the study.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and 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 (CQA) Department may conduct periodic audits of the study processes, including, but not limited to, auditing the clinical site, laboratories, vendors and CROs, the clinical database, and the final study report.

15 DATA HANDLING AND RECORD KEEPING

This study will use web-based, electronic case report forms (eCRFs) developed through a validated, Electronic Records/Electronic Signatures-compliant platform (US Title 21 CFR Part 11). Foamix Clinical Data Management department or designee will create the 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 Global Assessment Questionnaire

Question: “Considering your rosacea just before starting treatment and considering your condition today, indicate the change you have experienced according to the scale below”:

- 5 = Much better than prior to treatment
- 4 = Slightly better than prior to treatment
- 3 = Same as prior to treatment
- 2 = Slightly worse than prior to treatment
- 1 = Much worse than prior to treatment

APPENDIX 2: Subject Satisfaction Questionnaire

The following 8 questions will be asked of the subject at Visit 7 (Week 12 / Final Visit):

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

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

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

The answer to Question 8 will be selected from the following:

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