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 (FX2016-11)

ClinicalTrials.gov Identifier: NCT03142451

Date of Statistical Analysis Plan: 31 July 2018

Sponsor	*Foamix Pharmaceuticals*
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 (Study FX2016-11)*
Protocol Number:	*FX2016-11*
Premier Research PCN:	*FOAM166106*
Document Version:	*Final Version 1.0*
Document Date:	*31-Jul-2018*

Approvals

Role	Signatures	Date (dd-mmm-2018)
Biostatistician	Print Name: PPD Sign Name: PPD	02-Aug-2018 | 18:25:22 EDT
Foamix Pharmaceuticals Representative	PPD	02-Aug-2018 | 16:19:41 EDT

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Foamix Pharmaceuticals protocol number FX2016-11 (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), Version 3 dated 12 May 2017. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to the collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration, European Medicines Agency, and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to study FX2016-11.

Subjects who complete the Week 12 study visit may be invited to continue in an open-label extension study of FMX103 1.5% minocycline foam (protocol FX2016-13) for an additional 40-week treatment period. Analyses for FX2016-13 are reported separately.

2. Study Objectives and Endpoints

2.1. Study Objectives

The objectives of this 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.

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Incidence, severity, and causality of any adverse events (AEs), treatment-emergent AEs (TEAEs), serious TEAEs (SAEs), treatment-related TEAEs, and TEAEs leading to study discontinuation
- Changes from baseline in vital signs, laboratory parameters, and physical examinations
- Assessment of local signs and symptoms assessments, including erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, pealing/desquamation, and hyperpigmentation

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The co-primary efficacy endpoints of this study are:

- The absolute change from Day 0/Baseline in the inflammatory lesion count at Week 12
- Investigator Global Assessment (IGA) Treatment Success (dichotomized as yes/no) at Week 12, where success is defined as an IGA score of 0 (clear) or 1 (almost clear), and at least a 2-step improvement (decrease) from Day 0/Baseline

2.2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

- 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 from Day 0/Baseline in the inflammatory lesion count at Week 12
- The absolute change from Day 0/Baseline in the inflammatory lesion count and IGA Treatment Success at the interim visits at Weeks 4 and 8

2.2.2.3. [redacted]

[redacted]:

- [redacted]

3. Overall Study Design and Plan

3.1. Overall 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 rosacea over 12 weeks. Subjects with qualifying inflammatory lesion counts and IGA of rosacea severity scores will be enrolled and randomly assigned in a 2:1 ratio (active:vehicle) to receive 1 of the following 2 treatments:

- FMX103 1.5% minocycline foam
- Vehicle foam

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

Subjects will return for in-person visits at Weeks 2, 4, 8, and 12. At the discretion of the clinic staff and for the convenience of subjects or clinic staff, visits can be scheduled to occur 3 days before or after the nominal scheduled date for the Weeks 2, 4, and 8 visits and 3 days before or 5 days after for the Week 12 visit. Efficacy evaluations (inflammatory lesion counts and IGA) will be performed at Screening/Baseline and at Weeks 4, 8, and 12 during the study. An early follow-up telephone call will be made 1 week after the baseline clinic visit to review study procedures and record concomitant medications and AEs. For subjects who presented with new or on-going AEs and do not participate in study FX2016-13 (open-label extension study), a safety telephone call will be made 4 weeks after the Week 12 clinic visit to follow-up on these AEs and record any new concomitant medications.

3.2. Sample Size and Power

In Phase 2 Study FX2015-10, the proportion of subjects with an IGA score of 0 or 1 after CCI of treatment was CCI in the FMX103 1.5% dose group compared to CCI for the vehicle dose group. Table 5 in the protocol 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 2-sided test with a 0.05 level of significance. The sample size was calculated based on Fisher's exact test.

Assuming a CCI dropout rate and a 2:1 randomization, CCI subjects receiving FMX103 1.5% and CCI subjects receiving vehicle will provide at least 90% power to demonstrate a statistically significant difference in IGA success (ie, score of 0 or 1) between treatment groups.

For the co-primary endpoint of change from Day 0/Baseline to Week 12 in inflammatory lesion count, in the Phase 2 study, the FMX103 1.5% dose group had a mean reduction of CCI lesions, whereas the vehicle had a mean reduction of CCI lesions. The standard deviation (SD) was CCI.

For 90% power, CCI and CCI 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 CCI and CCI subjects in the FMX103 1.5% and vehicle groups, respectively.

3.3. Study Population

The study population comprises healthy male and non-pregnant females aged ≥18 years with a clinical diagnosis of moderate-to-severe facial papulopustular rosacea.

3.4. Treatments Administered

This is a double-blind study with 2:1 randomization between FMX103 1.5% and vehicle foam. FMX103 1.5% and vehicle will be supplied in identical canisters. Treatments will be administered daily for 12 weeks. The description of study drug kits and treatments is shown in Table 2 of the protocol. The dosing regimen is the same for both treatment groups.

3.5. Method of Assigning Subjects to Treatment Groups

During the baseline visit, subjects are randomly assigned to treatment using the interactive response technology (IRT) system. 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. Kits are dispensed at the Day 0/Baseline, Week 4, and Week 8 clinic visits.

3.6. Blinding and Unblinding

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 that each subject receives will not be disclosed to the Investigator, study site personnel, subjects, monitors, or 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 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 managed effectively 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 notified immediately 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 (ET) Visit (ie, Visit 5 [Week 12]) assessments will be completed.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

Assessment or Procedure	Screening	Day 0 / Baseline[a]	Visits/Early Follow-up				Final Visit[b]	Safety Follow-up[f]
Visit		**1**	**EF**	**2**	**3**	**4**	**5**	
Week			**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

a. Day 0/Baseline must occur within 45 days of Screening. Blood test results must not show clinically significant abnormalities.

b. If a subject withdraws from the study prematurely, all evaluations described under Visit 5/Week 12 (Final Visit) must be performed at an Early Termination Visit.

c. Height to be measured only at Day 0/Baseline.

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

e. 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.

f. A safety follow-up telephone call will be made 4 weeks after Visit 5/Week 12 (Final Visit) only for those subjects who do not participate in study FX2016-13 (open-label study) and presented with either new or ongoing adverse events at Visit 5/Week 12 (Final Visit).

AD-ST-33.04 Effective date: 30-Jun-2017

4. Statistical Analysis and Reporting

Statistical analysis will be performed following Premier Research's standard operating procedures.

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS® software (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used and for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects with non-missing values, mean, SD, median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category for each possible value. Missing responses will be enumerated, unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and p values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests.

4.2. Interim Analysis and Data Monitoring

No interim analyses are planned.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The SAF Population includes all randomized subjects who use at least 1 dose of study drug, including subjects who have no post-baseline assessments. Analyses using the Safety Population will be based on treatment received.
- **Intent-To-Treat Population (ITT):** The ITT Population includes all randomized subjects. Analyses using the ITT Population will be based on randomized treatment.

- **Per-Protocol (PP)**: The PP Population is defined as the subset of the ITT population without any protocol deviations that may have an impact on the efficacy assessments. Analyses using the PP Population will be based on randomized treatment.

  Subjects to be included in the PP Population will be determined by the Sponsor/contract research organization prior to the unblinding of the study. A subject with a protocol deviation whose severity is classified as 'Not Evaluable' per the Protocol Deviation Guidance Plan for protocol FX2016-11 will be excluded from the PP Population.

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

  - Failure to meet inclusion/exclusion criteria
  - Have been administered any interfering concomitant medications
  - Have not been compliant with the treatment regimen (eg, less than 80% compliant)
  - Did not complete Week 12 efficacy assessments
  - 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.

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

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last non-missing value prior to the first application of study drug will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Study Day

Day 1 is defined as the date of first study drug administration. Study day is calculated relative to the date of Day 1.

6.1.3. Adjustments for Covariates

Analysis centers (see Section 6.1.7, Pooling of Sites) will be taken into account either by including it as a blocking factor in the analysis of covariance (ANCOVA) model or by conducting the categorical analysis stratified by analysis center in the Cochran-Mantel-Haenszel (CMH) test.

In addition to analysis centers, baseline inflammatory lesion count will be included as a covariate in the ANCOVA for the change in inflammatory lesion count.

No other covariates will be included in the analyses of the co-primary endpoints.

6.1.4. Multiple Comparisons

No adjustments will be made for multiple comparisons of endpoints.

6.1.5. Handling of Dropouts or Missing Data

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 deal with missing data for inflammatory lesion counts and IGA, including:

- multiple imputation (MI)
- last observation carried forward (LOCF)
- baseline observation carried forward (BOCF)

The MI method will be the imputation used for the primary analysis. Sensitivity analyses using LOCF and BOCF will be performed to assess the robustness of alternate imputation assumptions.

No variables that have missing values other than inflammatory lesion counts and IGA will be imputed.

All analyses using the PP Population will use the observed cases (OC) approach; there will be no imputation for missing data at any time point. No other imputations will be made unless otherwise specified.

The imputation procedures for post-baseline missing inflammatory lesion counts and missing IGA scores are as follows:

- LOCF: The last observed value will be carried forward for any subsequent missing values. Baseline values will not be carried forward.
- BOCF: The baseline value will be used for any missing post-baseline values.
- MI: Multiple imputations is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data

given the observed data and covariates, creating multiple completed data sets. These completed datasets can then be analyzed using standard analysis methods.

6.1.5.1. MI Procedures for Inflammatory Lesion Counts

Intermittent missing value of inflammatory lesion counts will be imputed separately for each treatment group using the Markov Chain Monte Carlo (MCMC) method. Ten copies of the dataset with a monotonic missing pattern will be generated using the monotone data augmentation method[4,5] to impute the amount of missing data that is required to make the missing data pattern monotone before applying the multiple imputation algorithm. This method uses a non-informative Jeffreys prior to derive the posterior mode from the expectation-maximization algorithm as the starting values for the MCMC method. For each of the 10 monotonic missing pattern datasets, an additional 10 datasets will be imputed to replace missing values at scheduled visits (Weeks 4, 8, and 12) for a total of 100 datasets. These datasets will be generated using a regression-based multiple imputation model.[6] For subjects with complete data up to a particular visit, a multiple regression model will be fit that includes the outcome at that visit as the dependent variable and outcomes at previous visits and treatment group as independent variables. Using these regression models, a missing value for a subject at a particular visit will be imputed as a draw from the predictive distribution given the outcomes at previous visits (some possibly imputed) and treatment group.[6]

The SAS MI procedure (ie PROC MI) using the monotone regression method will be used. The ROUND option will be used to round the imputed values to the same precision as the observed values and the minimum value for imputed lesion counts will be specified as zero to avoid negative values. When an intended imputed value is less than the minimum, PROC MI will redraw another value for imputation. The ANCOVA analyses will be performed separately for each of the 100 complete analysis data sets, and the results will be combined into one multiple imputation inference (estimated treatment effect and associated confidence interval and p-value).[6, 7]

6.1.5.2. MI Procedures for IGA Treatment Success

The imputation of post-baseline IGA scores will be performed following a similar approach as described previously for inflammatory lesion counts. Intermittent missing IGA scores will be imputed separately for each treatment group where 10 copies of the dataset with monotonic missing pattern will be generated. For each of the 10 datasets, missing values at scheduled visits (Weeks 4, 8, and 12) will be imputed 10 more times using scores at the previous scheduled visits, creating a total of 100 copies of a full dataset. The logistic regression method for monotone data will be used for imputation. The CMH analyses will be performed separately for each of the 100 complete analysis sets and the risk ratios resulting from each imputed dataset will be log-transformed to normalize prior to combining. The estimated $\log(Risk\ Ratio)$ and corresponding 95% CI will be back-transformed from the combined results.[8]

A pre-specified seed number of [redacted] CCI will be used in all imputation procedures as described previously.

6.1.6. Analysis Visit Windows

All visit-based variables for this study will be analyzed according to their windowed visits defined by actual study day (see Table 2 below). Scheduled visits will be selected over unscheduled visits.

For those subjects who discontinue early from the study, Table 2 will be used to assign the appropriate analysis visit.

The study day (relative to first dose of study drug) will be calculated for each scheduled or ET visit and compared to the lower and upper bounds presented in Table 2 to define the visit window used for analyses. The analysis visit windows only apply to those visits that are applicable to the specific assessment. For example, if the scheduled or ET visit falls at Week 2 but a specific assessment was not scheduled at that visit (see Table 1, Schedule of Events), then that assessment will not be used.

The following analysis visit windows will apply:

Table 2: Analysis Visit Windows

Analysis Visit	Analysis Visit Name	Target Day of Planned Visit	Assessment Window (Days)
2	Week 2	14	Post-dose – 20
3	Week 4	28	21 – 41
4	Week 8	56	42 – 69
5	Week 12	84	70 – 97

If more than 1 visit occurs within a single visit window, then the analysis will use the visit closest to the target day. If 2 visits within the same visit window are equidistant from the target day, then the analysis will use the later visit.

6.1.7. Pooling of Sites

Analysis by investigative site will not be conducted, except for subject disposition.

However, investigative sites will be taken into account either by including it as a blocking factor in the ANCOVA model or by conducting the categorical analysis stratified by investigational site in the CMH test. If a site has randomized at least 30 subjects and has at least 16 subjects assigned to the FMX103 1.5% group and at least 8 subjects assigned to the vehicle group, then this site

satisfies the criteria of an 'analysis center.' Otherwise, the site is considered as a small site. To make up analysis centers from the small sites, the following approach will be followed:

(1) Small sites are ordered by site number,
(2) From the first site into the next site, the number of subjects randomized to each treatment group and total are added together until the pooled sites meet the criteria of an 'analysis center.'
(3) If there is (are) small site(s) left, the left over small sites(s) is (are) added to the last 'analysis center.'

An unspecified number of small sites can be combined to meet the criteria of an 'analysis center' until the pre-specified criteria are met. These analysis centers will be used for statistical analyses.

6.1.8. Derived Variables

- Total number of inflammatory lesion count = number of papules + number of pustules + number of nodules in all facial areas (forehead, left and right cheeks, nose, and chin)

- Change from baseline in inflammatory lesion count = (value at baseline) – (post-baseline value)

  Thus, a positive change will reflect a reduction in inflammatory lesion count. Change from baseline will be calculated at the following time points: 4, 8, and 12 weeks.

- Percentage change from baseline inflammatory lesion count =

$$100 \times \frac{value\ at\ baseline - post\ baseline\ value}{value\ at\ baseline}$$

  Thus, a positive percentage change will reflect a reduction in inflammatory lesion count. The percentage change from baseline will be calculated at the following time points: 4, 8, and 12 weeks.

- TEAE = any adverse event with an onset date on or after the first application of study drug and before the last application of study drug plus 3 days having been absent pre-treatment or worsening relative to the pre-treatment state (for subjects not participating in the FX2016-13 open-label extension study), or events reported through the Week 12 clinic visit (for subjects participating in the extension study).

- Body mass index (kg/m^2) = $\frac{weight\ in\ kilograms}{(height\ in\ meters)^2}$

- Age groups Age group=1 if 18≤ age (full years) ≤ 40
  Age group=2 if 41≤ age (full years) ≤ 64
  Age group=3 if 65≤ age (full years)
- Treatment duration (days) =

  Date of last dose of study drug – Date of first dose of study drug + 1 day

  For subjects who are missing the date of last study drug application, the last known contact date will be used in the calculation of treatment duration and study drug exposure.

- Study drug exposure (days) =

  Treatment duration (days) – Number of days that a subject reported missing a dose (between the date of first and last dose)

- Compliance (%) = 100 x Study drug exposure (days) / Treatment duration (days)

  Study drug compliance will not be calculated for subjects whose date of last study drug application is unknown.

- Days on incorrect study drug = Date of correct drug re-dispense – Date of incorrect study drug dispensation

  Percent duration on incorrect drug (%) = 100 x Days on incorrect study drug (days) / Treatment duration (days)

  Derivations only apply to subjects who were dispensed incorrect kits with inconsistent treatment regimen, if this occurs over the course of this study. Date of study drug application is assumed to be the date of dispensation. Percent duration on incorrect drug is used, if applicable, in determining the "actual" treatment group to which a subject will be assigned for purposes of analyzing safety data (see Sections 6.1.9 and 9).

- IGA treatment success = yes if the following conditions are both satisfied:
  - IGA score of 0 or 1
  - at least a 2-grade improvement (decrease) from baseline

  Otherwise the IGA treatment success = no

- IGA treatment success-secondary = yes if the subject has at least a 2-grade improvement (decrease) from baseline, otherwise the IGA treatment success = no

6.1.9. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but rather will be included in the data listings.

All p-values will be displayed in 4 decimals and rounded using standard scientific notation (eg, 0.xxxx). If a p-value less than 0.0001 occurs it will be shown in tables as <0.0001.

If during the course of this study it is determined that subjects were inadvertently dispensed incorrect kits, the following criteria will be used to determine treatment group for safety analyses: Subjects who were exposed to the study drug that they had not been randomized for ≥ 20% of their treatment duration will be included in the FMX103 1.5% group for all safety assessments. Subjects who were exposed to the study drug for which they had not been randomized for < 20% of their treatment duration will be assessed according to the treatment they actually received for the majority of the study.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. In general, a TEAE is defined as an AE with an onset date on or after the first application of study drug and before the last application of study drug plus 3 days (for subjects not participating in the FX2016-13 open-label extension study), or events reported through the Week 12 clinic visit (for subjects participating in the extension study). For subjects missing the date of last study drug application due to being lost to follow-up (LTFU), or for any other reason, any AE with an onset date after the first study drug application with be considered a TEAE.

Any AE that started before the first dose of study drug and worsens in severity or changes from nonserious to serious on or after the first dose date will also be designated as a TEAE. If an event worsens in severity during the study, the outcome of the lower grade event would be RECOVERED/RESOLVED or RECOVERED/RESOLVED WITH SEQUELAE with an end date (of that grade). A new event is recorded on the AE case report form (CRF) with a start date that matches the end date, and the term recorded includes “Worsened” (eg, “Worsened Headaches”). If an event becomes serious, the date that the event became serious is recorded on the AE CRF as the End Date of that AE and the Start Date of the corresponding SAE.

For subjects participating in the extension study, AEs and concomitant medications that are ongoing as of the Week 12 visit will be closed out with a stop date of “ongoing.” Adverse events and concomitant medications that are continuing from this study will be copied into the extension study database with start dates entered as the original start date from this study.

A treatment-related AE is any AE with a relationship to the study drug of possible or probable.

Adverse events or medications with missing complete start dates will be classified as treatment emergent or concomitant, as appropriate.

For analysis purposes, an AE that does not have a recorded relationship to the study drug value will be considered as “Probably Related” to the study drug unless the start date of the AE is

before the date of first study drug administration, in which case the event would be considered as "Unlikely Related." If the severity of an AE is missing, the severity will be considered as "Missing."

If partial AE or concomitant medication onset dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later; if just month is missing then the month assigned is the month of the first dose, unless that results in a date prior to the first dose in which case the month after the first dose is used; and if both month and day are missing then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later.

These conventions will be applied only to onset dates with the following precaution related to AE onset dates: if the missing date reflects the date of onset of an AE, the modified date will be constructed to match the first documented date post drug administration while preserving the order in which the AE was reported in the case report form (CRF).

For partial end dates, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if only the day is missing, then the day is assigned the last day of the month; if both day and month are missing, they are assigned the last day of the year (31 Dec).

For subjects who are missing the date of last study drug application, for any reason, the last known contact date will be used in the calculation of treatment duration and study drug exposure. Study drug compliance will not be calculated for those subjects whose date of last study drug application is unknown.

For analysis purposes, repeat laboratory test results will not be used unless the original laboratory value is missing or indicated as invalid, in which case the first non-missing repeat laboratory value will be used for data analysis.

7. Study Subjects and Demographics

7.1. Disposition of Subjects and Withdrawals

The number and percentage of subjects who are included in each analysis population, who complete the study, who participate in study FX2016-13 (open-label extension study), withdraw from the study (overall and by reason for withdrawal), and who are excluded from the PP Population (overall and by reason for exclusion) will be summarized overall and by treatment group. The overall number of subjects who were screened will also be presented.

A by-subject enrollment and disposition listing will be presented for all randomized subjects. Subjects who are screen failures will be presented in a separate listing.

Percentages and counts will be calculated using randomized subjects, where applicable.

7.2. Protocol Deviations

Protocol deviations will be listed for all randomized subjects.

7.3. Demographics and Other Baseline Characteristics

Summary statistics of demographics and baseline characteristics will be summarized overall and by treatment group. The following demographic and baseline variables will be included:

- Age (years)
- Age group in full years (18 to 40 years, 41 to 64 years, ≥ 65 years)
- Sex
- Race
- Ethnicity
- Baseline body weight (kg), height (cm), and body mass index (BMI) (kg/m^2)
- Baseline inflammatory lesion count
- Baseline IGA score (moderate=3, severe=4)

For continuous variables, the number of non-missing values and the mean, SD, minimum, median, and maximum will be tabulated.

For categorical variables, the counts and proportions of each value will be tabulated. Subjects reporting more than 1 race will be included in a "More than one race" category for purposes of tabulating summary statistics.

These analyses will be conducted for the ITT, PP, and Safety Populations.

Past medical histories for all randomized subjects will be provided in a by-subject listing.

7.4. Study Drug Exposure and Compliance

The following parameters of study drug exposure and compliance will be summarized by randomized treatment group for the ITT and PP Populations:

- Treatment duration (days)
- Study drug exposure (days)
- Study drug compliance (%)

For a given day, a subject is considered compliant with treatment if any amount of study drug is applied to the facial area. For subjects who are missing the date of last study drug application, for any reason, the last known contact date will be used in the calculation of treatment duration and study drug exposure. Study drug compliance will not be calculated for those subjects whose date of last study drug application is unknown.

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

To attain the primary efficacy goal of FMX103 1.5% being considered superior to vehicle, both co-primary efficacy endpoints must be significant (ie, attaining significance at the 2-sided 0.05 level without adjustment for multiplicity).

The null hypotheses of the equality of FMX103 1.5% and vehicle are as follows:

- H_{01}: the absolute changes from baseline in inflammatory lesion count at Week 12 in the 2 treatment groups are equal
- H_{02}: the IGA success rates at Week 12 in the 2 treatment groups are equal

The primary efficacy analyses will be based on the ITT Population using MI and are as follows:

- Absolute change from baseline in inflammatory lesion count:

  For each of the multiple imputed datasets, change from baseline in inflammatory lesion count will be analyzed using an ANCOVA model, with treatment as a main effect, baseline inflammatory lesion count as a covariate, and analysis center as a blocking factor. These results will be combined with the SAS MIANALYZE procedure (ie, PROC MIANALYZE) using Rubin's formula and the resulting p-value will be used for inference at the 0.05 level of significance[8]. The combined estimated mean difference in change from baseline (FMX103 1.5% minus vehicle) and the associated 95% CI will be reported.

- Dichotomized IGA Success Rate:

  For each of the multiple imputed datasets, the dichotomized IGA (yes/no) will be analyzed using a CMH test, stratified by analysis center. These results will be combined in Proc MIANALYZE and the resulting p-value will be used for inference at the 0.05 level. The combined estimated $\log(Risk\ Ratio)$ of FMX103 1.5% vs. vehicle foam, and associated 95% confidence limits will be back-transformed. The combined Mantel-Haenszel risk ratio, along with its estimated standard error (SE), 95% CI, and the associated p-value will be reported.

  If the overall IGA Treatment Success rate is less than 10%, the simple proportion of responders in each treatment group, the proportion difference, along with the estimated SE will be reported and combined in Proc MIANALYZE. The resulting p-value, proportions, proportion difference, and their 95% CIs will be presented.

Sensitivity analyses of the co-primary efficacy endpoints will be performed using the same analysis methods described previously. Sensitivity analyses will include:

- ITT Population (OC, LOCF, and BOCF)
- PP Population (OC)

Homogeneity among analysis centers will be assessed by including an analysis center by treatment interaction in the ANCOVA model of the ITT OC analysis of the absolute change from baseline in inflammatory lesion counts. Analysis center by treatment interaction will be tested at the 0.1 level, and if significant, will further be explored.

To account for the possibility of extreme outliers in the analysis of lesion counts, a sensitivity analysis will be conducted on the primary endpoint of absolute change from baseline in inflammatory lesion counts at Week 12 using multiple imputation in which the data will be rank-transformed prior to analysis.

8.2. Secondary CCI Efficacy Analysis

Descriptive summaries will be used to summarize all endpoints, including secondary CCI endpoints, for each visit:

- absolute CCI change from baseline in inflammatory lesion count
- dichotomized IGA score, where success is defined as a 2-step improvement in score at Week 12 compared to baseline.

Secondary CCI efficacy endpoints will be analyzed similarly to the appropriate co-primary efficacy parameter.

Secondary CCI efficacy endpoints will be tested at the 0.05 level of significance, only if both co-primary efficacy endpoints are significant in the primary analyses.

8.3. Subject Satisfaction Questionnaire

Answers to the Subject Satisfaction Questionnaire will be summarized for Week 12 (or the ET visit) using frequency counts and percentages by randomized treatment group for the ITT Population.

8.4. Subject Global Assessment

Responses from the Subject Global Assessment (SGA) questionnaire will be summarized for Weeks 2, 4, 8, and 12 using frequency counts and percentages by randomized treatment group for the ITT Population.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported TEAEs, changes in clinical laboratory values, changes in vital signs, physical examination results, and local signs and symptoms assessments.

All safety analyses will be performed on the Safety Population. Subjects will be reported according to the treatment they actually received. If during the course of this study it is determined that subjects were inadvertently dispensed incorrect kits, the following criteria will be used to determine treatment group for the safety analyses: Subjects who were exposed to the study drug that they had not been randomized for ≥ 20% of their treatment duration will be included in the FMX103 1.5% group for all safety assessments. Subjects who were exposed to the study drug for which they had not been randomized for < 20% of their treatment duration will be assessed according to the treatment they actually received for the majority of the study.

Safety assessments will be summarized using descriptive statistics by treatment group and in individual subject listings.

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

9.1. Adverse Events

All AE terms will be coded using MedDRA, Version 20.0.

All AEs that occur after informed consent but before administration of the study drug will be recorded as medical history. If relationship to treatment is missing, the event will be summarized conservatively as probably related to study drug unless the start date of the AE is before the date of first study drug administration, in which case the event would be considered as not related. If severity is missing, the event will be summarized conservatively as severe. Through the data cleaning process, all attempts will be made to avoid missing values for relationship and severity.

All TEAEs will be summarized by system organ class (SOC) and preferred term (PT) and sorted in order of descending frequency of the SOC and then by descending frequency order (total across treatment groups) of the PT within each SOC.

An overall summary of AEs will be presented by treatment group. This summary will include the total number of events, frequency counts, and percentages for:

- Any AEs
- Any TEAEs
- Any SAEs
- Any treatment-related TEAEs
- Any TEAE leading to study discontinuation
- TEAEs resulting in death

Summaries of the incidence of TEAEs and SAEs will be displayed by treatment group and by:

- SOC and PT
- SOC, PT, and maximum severity (mild, moderate, severe)
- SOC, PT, and maximum causality (not related, related) to the study drug

If there are multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each PT. In the summaries showing severity and relationship to the study drug, the event with the maximum severity or strongest relationship will be reported.

All AEs will be presented in a by-treatment and by-subject listing, detailing the verbatim term given by the Investigator, the PT, SOC, onset date and time, end date and time, severity, outcome, relationship to study drug, action taken with study drug, other action taken, seriousness, and criteria for seriousness. All SAEs will be presented in a separate listing.

9.1.1. Adverse Events Leading to Withdrawal

The incidence (frequencies and percentages) of TEAEs leading to withdrawal of study drug by treatment group, SOC, and PT will be summarized for the Safety Population. Summaries will also be presented by maximum severity and by maximum causality.

A data listing of AEs leading to withdrawal of the study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and tabulated by SOC and PT and presented by treatment group. All SAEs will also be presented by maximum severity and by maximum causality.

9.2. Clinical Laboratory Evaluations

Absolute values and changes from baseline will be summarized by treatment group for clinical laboratory (chemistry and hematology) results using descriptive statistics. The number of subjects with clinical laboratory values below, within, or above the normal range will be tabulated for each clinical laboratory test by time point. Shift tables for each clinical laboratory test will cross-tabulate the number of subjects with values below the laboratory reference range (low), values within the laboratory reference range (normal), or above the laboratory range (high) at baseline with the number of subjects with low, normal or high values at each post-baseline time point. Normal ranges and values outside the normal ranges will be identified by the central laboratory. A separate listing of out of normal range laboratory results will be provided.

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

Urinalysis and urine pregnancy test results will be presented in by-subject listings.

9.3. Vital Signs

Descriptive summaries of actual values and changes from baseline by treatment group will be presented for systolic and diastolic blood pressure, heart rate, and body weight. Height and BMI will be summarized at baseline only.

9.4. Physical Examinations

Physical examinations will be summarized using descriptive statistics for baseline and each post-baseline time point by treatment group. Shifts from baseline will also be summarized.

Abnormal physical examination findings will be displayed in a by-subject listing.

9.5. Local Signs and Symptoms Assessments

Erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation at the sites of study drug application will be assessed at each study visit. All signs/symptoms with the exception of erythema will be graded on a 0 to 3 scale (0=none; 1=mild; 2=moderate; 3=severe). Erythema will be graded on a 0 to 4 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). Itching will be assessed on the same 0 to 3 scaled based on the subjects' subjective assessment.

The severity of erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation will be summarized using frequency counts and percentages at each visit by treatment group.

9.6. Prior and Concomitant Medication

A concomitant medication is any non-protocol specified drug or substance administered during participation in the study, including medications that are ongoing at the time of informed consent. For subjects not continuing into the FX2016-13 open-label extension study, this period of participation is from the first day of screening through the last contact at 4 weeks after the Week 12 clinic visit. For subjects continuing into the extension study, this period is from the first day of screening through the Week 12 clinic visit.

Prior and concomitant medications will be summarized descriptively by treatment group and overall using counts and percentages in each Anatomical Therapeutic Chemical (ATC) level 2 group and PT (ie, generic name) for the ITT, PP, and Safety Populations.

Prior medications will be presented separately from concomitant medications. Medications that started prior to Day 1 will be considered prior medications whether or not they were stopped prior to Day 1. Any medications continuing or starting after Day 1 will be considered to be concomitant. If a medication starts prior to Day 1 and continues after Day 1 it will be considered both prior and concomitant.

- Medications will be coded using the World Health Organization Drug Dictionary Version March 2017.

10. Changes from Planned Analysis

The protocol specifies that 'analysis centers' will be defined as sites, or groups of sites, that have at least 8 randomized subjects. Based on the proposed analysis strategy for IGA treatment success, this definition has been revised such that an analysis center is a site, or group of smaller sites, that has at least 30 subjects and has at least 16 subjects assigned to the FMX103 1.5% group and at least 8 subjects to the vehicle group. This will minimize the likelihood of zero-cell counts in the CMH test.

11. Other Planned Analysis

11.1. Pharmacokinetic Analysis

No pharmacokinetic analysis is planned for this study.

12. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm

3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf

4. Li KH (1988) Imputation using Markov chains. J Statist Comp Simul; 30:57-79.

5. Liu C (1993) Bartlett's decomposition of the posterior distribution of the covariance for normal monotone ignorable missing data. J Mult Anal; 46:198-206.

6. Little R, Yau L (1996) Intent-to-treat analysis for longitudinal studies with drop-outs. Biometrics; 52:1324-1333.

7. Schafer, JL (1997) Analysis of Incomplete Multivariate Data, New York: Chapman and Hall.

8. Rubin, D.B (1987). Multiple Imputation for Nonresponse in Surveys. New York. John Wiley & Sons.

13. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the Sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (ie, listing number where applicable).

14. Planned Table Descriptions

The following are planned summary tables for protocol FX2016-11. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

Table 3: Disposition, Demographic, Prior Medications, and Study Drug Exposure Data Summary Tables

Table Number	Population(s)	Table Title / Summary	Supporting listing
14.1 Disposition, Demographic, Prior Medications, and Study Drug Exposure Data			
Table 14.1.1	All Subjects	Summary of Subject Enrollment and Disposition	16.2.1.1 16.2.1.2 16.2.1.3 16.2.3.1
Table 14.1.2	ITT, PP, SAF	Summary of Demographics and Baseline Characteristics	16.2.4.1 16.2.6.1 16.2.6.2
Table 14.1.3	ITT, PP, SAF	Summary of Prior Medications by ATC Level 2 and Preferred Term	16.2.4.3
Table 14.1.4	ITT, PP	Summary of Study Drug Exposure	16.2.5.1
Table 14.1.5	ITT, PP	Summary of Subject Enrollment by Analysis Center	16.2.1.1
Table 14.1.6	ITT, PP	Study Drug Compliance	16.2.5.2

Table 4: Efficacy Data

Table Number	Population(s)	Table Title / Summary	Supporting listing
14.2 Efficacy Data			
Table 14.2.1.1	ITT, PP	Descriptive Summary of Inflammatory Lesion Count	16.2.6.2
Table 14.2.1.2	ITT, PP	Descriptive Summary of IGA Treatment Success	16.2.6.1
Table 14.2.2.1	ITT	Analysis of Change from Baseline in Inflammatory Lesion Count - Multiple Imputation	16.2.6.2
Table 14.2.2.2	ITT	Analysis of IGA Treatment Success - Multiple Imputation	16.2.6.1
Table 14.2.3.1	ITT	Analysis of Change from Baseline in Inflammatory Lesion Count - LOCF	16.2.6.2
Table 14.2.3.2	ITT	Analysis of Change from Baseline in Inflammatory Lesion Count - BOCF	16.2.6.2
Table 14.2.3.3	ITT, PP	Analysis of Change from Baseline in Inflammatory Lesion Count - Observed Cases	16.2.6.2
Table 14.2.3.4	ITT, PP	Analysis of Percent Change from Baseline in Inflammatory Lesion Count - Observed Cases	16.2.6.2
Table 14.2.3.5	ITT	Analysis of Ranked Change from Baseline in Inflammatory Lesion Count -Multiple Imputation	16.2.6.2
Table 14.2.3.6	ITT	Analysis of Change from Baseline in Inflammatory Lesion Count - Analysis Center Interaction – Observed Cases (Week 12)	16.2.6.2
Table 14.2.4.1	ITT	Analysis of IGA Treatment Success - LOCF	16.2.6.1
Table 14.2.4.2	ITT	Analysis of IGA Treatment Success - BOCF	16.2.6.1
Table 14.2.4.3	ITT, PP	Analysis of IGA Treatment Success - Observed Cases	16.2.6.1
Table 14.2.4.4	ITT	Analysis of IGA Treatment Success-Secondary - Observed Cases	16.2.6.1
Table 14.2.5	ITT	Descriptive Summary of Subject Global Assessment	16.2.6.4
Table 14.2.6	ITT	Descriptive Summary of Subject Satisfaction Questionnaire	16.2.6.3

Table 5: Safety Data

Table Number	Population(s)	Table Title / Summary	Supporting listing
14.3 Safety Data			
14.3.1 Displays of Adverse Events			
Table 14.3.1.1	SAF	Summary of All Adverse Events	16.2.7.1
Table 14.3.1.2	SAF	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	16.2.7.1
Table 14.3.1.3	SAF	Treatment-Emergent Adverse Events by Severity, System Organ Class, and Preferred Term	16.2.7.1
Table 14.3.1.4	SAF	Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term	16.2.7.1
14.3.2 Other Serious and Significant Adverse Events			
Table 14.3.2.1	SAF	Serious Adverse Events by System Organ Class and Preferred Term	16.2.7.2
Table 14.3.2.2	SAF	Serious Adverse Events by Severity, System Organ Class, and Preferred Term	16.2.7.2
Table 14.3.2.3	SAF	Serious Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term	16.2.7.2
Table 14.3.2.4	SAF	Adverse Events Leading to Withdrawal from the Study by System Organ Class and Preferred Term	16.2.7.3
Table 14.3.2.5	SAF	Adverse Events Leading to Withdrawal from the Study by Severity, System Organ Class, and Preferred Term	16.2.7.3
Table 14.3.2.6	SAF	Adverse Events Leading to Withdrawal from the Study by Relationship to Study Drug, Systemic Organ Class, and Preferred Term	16.2.7.3

Table Number	Population(s)	Table Title / Summary	Supporting listing
14.3.5 Laboratory Data Summary Tables			
Table 14.3.5.1	SAF	Clinical Chemistry Results	16.2.8.1
Table 14.3.5.2	SAF	Shift Table of Clinical Chemistry Results	16.2.8.1
Table 14.3.5.3	SAF	Hematology Results	16.2.8.2
Table 14.3.5.4	SAF	Shift Tables of Hematology Results	16.2.8.2
14.3.6 Other Safety and Tolerability Summary Tables			
Table 14.3.6.1	SAF	Shift Table of Physical Examination Results	16.2.9.2
Table 14.3.6.2	SAF	Vital Sign Results	16.2.9.1
Table 14.3.6.3	SAF	Concomitant Medications by ATC Level 2 and Preferred Term	16.2.9.3
Table 14.3.6.4	SAF	Summary of Local Signs and Symptoms Assessments	16.2.9.4

14.1. Planned Listing Descriptions

The following are planned data and subject data listings for protocol FX2016-11.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, analysis center, site, and subject number. Calculated variables will be included in the listings, as applicable.

In all listings, a blank line will be placed between each subject. Within a data listing, if an item appears line after line (eg, repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 6: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2 Subject Data Listings **16.2.1 Subject Discontinuations/Completions**		
Data listing 16.2.1.1	All Randomized Subjects	Assignment to Analysis Populations and Treatment Group
Data listing 16.2.1.2	All Randomized Subjects	Study Completion Status
Data listing 16.2.1.3	Screen Failures	List of Reasons for Screening Failure
16.2.2 Protocol Deviations		
Data listing 16.2.2.3	All Randomized Subjects	Protocol Deviations
16.2.3 Subjects Excluded from the Efficacy Analyses		
Data listing 16.2.3.1	All Randomized Subjects	List of Subjects Excluded from Analysis Populations

Data Listing Number	Population	Data Listing Title / Summary
16.2.4 Demographic Data and Other Baseline Characteristics		
Data listing 16.2.4.1	All Randomized Subjects	Demographic Data
Data listing 16.2.4.2	All Randomized Subjects	Medical History
Data listing 16.2.4.3	All Randomized Subjects	Prior Medications
16.2.5 Compliance Data		
Data listing 16.2.5.1	All Randomized Subjects	Study Drug Accountability
Data listing 16.2.5.2	All Randomized Subjects	Study Drug Compliance
16.2.6 Individual Efficacy Response Data		
Data listing 16.2.6.1	ITT	IGA Score
Data listing 16.2.6.2	ITT	Inflammatory Lesion Count by Facial Area
Data listing 16.2.6.3	ITT	Subject Satisfaction Questionnaire (SSQ)
Data listing 16.2.6.4	ITT	Subject Global Assessment (SGA)
16.2.7 Adverse Event Listings		
Data listing 16.2.7.1	SAF	Adverse Events
Data listing 16.2.7.2	SAF	Serious Adverse Events
Data listing 16.2.7.3	SAF	Adverse Events Leading to Withdrawal
Data listing 16.2.7.4	SAF	Deaths
16.2.8 Laboratory Data Listings		
Data listing 16.2.8.1	SAF	Clinical Chemistry Results
Data listing 16.2.8.2	SAF	Hematology Results
Data listing 16.2.8.3	SAF	Urinalysis Results

Data Listing Number	Population	Data Listing Title / Summary
Data listing 16.2.8.4	All Randomized Subjects	Clinically Significant Laboratory Tests for Hematology, Chemistry, and Urinalysis
Data listing 16.2.8.5	All Randomized Subjects	Out of Range (Abnormal) Laboratory Tests for Hematology, Chemistry, and Urinalysis
Data listing 16.2.8.6	SAF	Pregnancy Test Results
16.2.9 Other Clinical Observations and Measurements		
Data listing 16.2.9.1	SAF	Vital Signs
Data listing 16.2.9.2	SAF	Abnormal Physical Examination Results
Data listing 16.2.9.3	SAF	Concomitant Medications
Data listing 16.2.9.4	SAF	Local Signs and Symptoms Assessments
Data listing 16.2.9.5	SAF	Photography of the Face

14.2. Planned Figure Descriptions

There are no planned figures.

15. Tables, Listings, and Figure Shells

15.1. Standard Layout for all Tables, Listings, and Figures

Table and listing shells are provided in a separate document.

Note that programming notes may be added after each TLF shell if appropriate.

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BOCF	baseline observation carried forward
CI	confidence intervals
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
ET	early termination
IGA	Investigator's Global Assessment
IRT	interactive response technology
ITT	intent-to-treat
LOCF	last observation carried forward
LTFU	lost to follow-up
MCMC	Markov Chain Monte Carlo
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
OC	observed cases

Abbreviation	Definition
PP	per-protocol
PT	preferred term
SAE	serious adverse event
SAF	Safety
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SD	standard deviation
SGA	subject global assessment
SOC	system organ class
SSQ	subject satisfaction questionnaire
TEAE	treatment-emergent adverse event
TMF	trial master file

Statistical Analysis

Table and Listing Shells

Sponsor	*Foamix Pharmaceuticals*
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 (Study FX2016-11)*
Protocol Number:	*FX2016-11*
Premier Research PCN:	*FOAM166106*
Document Version:	*Final version 1.0*
Document Date:	*31-Jul-2018*

Table and Listing Shells for Foamix FX2016-11

14.1 Demographic Data Summary Tables

Table 14.1.1
Summary of Subject Enrollment and Disposition
All Subjects

Number of Subjects	FMX103 1.5%	Vehicle Foam	Overall
Number of subjects screened			xxx
Number of subjects in ITT population	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number of subjects in PP population	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number of subjects in SAF population	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number of subjects completing the study	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number of subjects participating in study FX2016-13 (open-label extension study)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number of subjects discontinued	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reason for discontinuation			
Adverse event	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Abnormal laboratory result	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Lost to follow-up	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Subject request	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Protocol deviation	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number of subjects excluded from PP population	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reason for exclusion			
Failure to meet inclusion/exclusion criteria	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Have administered any interfering concomitant medications	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not compliant with the treatment regimen	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Randomization error	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Note: Percentages are based on the number of subjects randomized. Randomized treatment groups are presented.

The Safety (SAF) population includes all randomized subjects who use at least 1 dose of study drug. Subjects who have no post-baseline assessments will be included unless all dispensed study drug is returned unused.

The Intent-to-treat (ITT) population includes all randomized subjects.

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

Source: Listing 16.2.1.1, 16.2.1.2, 16.2.1.3, 16.2.3.1

Table 14.1.2.x
Summary of Demographics and Baseline Characteristics
ITT Population

Variable	Sample Characteristics/Category	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)	Overall (N=xxx)
Age [years]	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min to Max	xx to xx	xx to xx	xx to xx
Body Weight [kg]	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min to Max	xx to xx	xx to xx	xx to xx
Body Height [cm]	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min to Max	xx to xx	xx to xx	xx to xx
Body Mass Index (BMI) [kg/m^2]	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min to Max	xx to xx	xx to xx	xx to xx
Age groups [full years] [1]	18 to 40	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	41 to 64	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	≥ 65	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx	xx	xx
Sex	Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx	xx	xx

Table 14.1.2.x (cont'd)

Variable	Sample Characteristics/Category	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)	Overall (N=xxx)
Ethnicity	Hispanic/Latino	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Non Hispanic/Latino	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx	xx	xx
Race	American Indian or Alaska native	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Asian	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Black or African American	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Native Hawaiian or other Pacific Islander	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	White	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	More than one race	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx	xx	xx
IGA Score	3	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	4	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing	xx	xx	xx
Inflammatory Lesion Count	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min to Max	xx to xx	xx to xx	xx to xx

Note: Percentages exclude missing data.
[1] Age (years) at the baseline visit.
Source: Listing 16.2.4.1, 16.2.6.1, 16.2.6.2

Programming Note: Table 14.1.2.1 for ITT Population; Table 14.1.2.2 for PP Population; Table 14.1.2.3 for Safety Population. For all tables that use the ITT or PP populations, include 'Randomized treatment groups are presented' in the note. For tables using the safety population, include 'Treatment groups presented are treatment received.'

Table 14.1.3.x
Summary of Prior Medications by ATC Level 2 and Preferred Term
ITT Population

ATC Level 2 Preferred Term [1]	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)	Overall (N=xxx)
Any prior medication	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ATC level 2 entry 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
...			
ATC level 2 entry 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PT 6	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ATC level 2 entry 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
...	...	...	...
..	..	..	..
.	.	.	.

Note: Percentages are 100*n/N. Subjects were counted only once for each Anatomical Therapeutic Chemical (ATC) or preferred term. Medications that started prior to Day 1 are considered prior whether or not they were stopped prior to Day 1.
[1] Medications were coded using WHO-DD (Enhanced version March 2017) ATC level 2. Preferred Term is ATC level 5.
Source: Listing 16.2.4.3

Programming Note: Table 14.1.3.1 for ITT Population; Table 14.1.3.2 for PP Population; Table 14.1.3.3 for Safety Population; For all tables that use the ITT or PP populations, include 'Randomized treatment groups are presented' in the note. For tables using the safety population, include 'Treatment groups presented are treatment received.' Whenever possible, keep all PT within an ATC level 2 on one page.

Table 14.1.4.x
Summary of Study Drug Exposure
ITT Population

Variable	Sample Characteristics	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)	Overall (N=xxx)
Treatment Duration (days) [1]	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min to Max	xx to xx	xx to xx	xx to xx
Total Days of Exposure [2]	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min to Max	xx to xx	xx to xx	xx to xx

Note: For subjects who are missing the date of last dose, the last known contact date will be used in the calculation of treatment duration and exposure.
[1] Treatment duration (days) is defined as the date of last dose of study drug minus the date of first dose of study drug plus 1 day.
[2] Total days of exposure is defined as the difference in treatment duration (days) and the number of days that a subject reported missing a dose (between the date of first and last dose).
Source: Listing 16.2.5.1

Programming Note: Table 14.1.4.1 for ITT Population; Table 14.1.4.2 for PP Population; For all tables that use the ITT or PP populations, include 'Randomized treatment groups are presented' in the note. For tables using the safety population, include 'Treatment groups presented are treatment received.'

Table 14.1.5.x
Summary of Subject Enrollment by Analysis Center
ITT Population

		Number of Subjects Randomized		
Analysis Center[1]	Sites	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)	Overall (N=xxx)
xxx	xxx/xxx	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
xxx	xxx/xxx/xxx	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Note: Percentages are 100*n/N.
[1] Analysis centers are sites, or groups of sites, that have randomized at least 30 subjects and have at least 16 subjects assigned to the FMX103 1.5% group and at least 8 subjects in the vehicle group.
Source: Listing 16.2.1.1

Programming Note: Table 14.1.5.1 for ITT Population; Table 14.1.5.2 for PP Population; For all tables that use the ITT or PP populations, include 'Randomized treatment groups are presented' in the note. For tables using the safety population, include 'Treatment groups presented are treatment received.'

Table 14.1.6.x
Study Drug Compliance
ITT Population

Statistic	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)	Overall (N=xxx)
n (# missing)	xx (xx)	xx (xx)	xx (xx)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min to Max	xx.x to xx.x	xx.x to xx.x	xx.x to xx.x

Note: Compliance (%) = 100 x Study drug exposure (days) / Treatment duration (days).
Subjects who are missing last dose dates are not included.
Source: Listing 16.2.5.2

Programming Note: Table 14.1.6.1 for ITT Population; Table 14.1.6.2 for PP Population; For all tables that use the ITT or PP populations, include 'Randomized treatment groups are presented' in the note. For tables using the safety population, include 'Treatment groups presented are treatment received.'

14.2 Efficacy Data

Table 14.2.1.1.x
Descriptive Summary of Inflammatory Lesion Count
ITT Population

Visit	Variable	Sample Characteristics	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
Baseline	Observed value	n (# missing)	xxx (xx)	xxx (xx)
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min to Max	xx to xx	xx to xx
Week 4	Observed value	n (# missing)	xxx (xx)	xxx (xx)
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min to Max	xx to xx	xx to xx
	Change from baseline [1]	n (# missing)	xxx (xx)	xxx (xx)
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min to Max	xx to xx	xx to xx
	Percent change from baseline [1]	n (# missing)	xxx (xx)	xxx (xx)
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min to Max	xx to xx	xx to xx

Programming Note: Continue for Weeks 8 and 12

[1] Change from baseline is calculated as the value at baseline minus the post-baseline value. Thus, a positive change will reflect a reduction in lesion count. The same definition is used in the numerator for percent change. Source: Listing 16.2.6.2

Programming Note: Table 14.2.1.1.1 for ITT Population; Table 14.2.1.1.2 for PP Population; For all tables that use the ITT or PP populations, include 'Randomized treatment groups are presented' in the note. For tables using the safety population, include

'Treatment groups presented are treatment received.' Round percent change to one additional decimal place over CHG. Keep each week on a single page.

Table 14.2.1.2.x
Descriptive Summary of IGA Treatment Success
ITT Population

		IGA Treatment Success[1]		IGA Treatment Success-Secondary[2]	
Visit	Score/ Category	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
Baseline [3]	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week 4	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week 8	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week 12	n (# missing)	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are based on the number of subjects with non-missing value (yes or no) at each visit.
[1] IGA Treatment Success is defined as an IGA of 0 or 1 and a 2-grade improvement in IGA from baseline.
[2] IGA Treatment Success-Secondary is defined as a 2-grade improvement (decrease) in IGA from baseline.
[3] Values presented are Baseline IGA score.
Source: Listing 16.2.6.1

Programming Note: Table 14.2.1.3.1 for ITT Population; Table 14.2.1.3.2 for PP Population; For all tables that use the ITT or PP populations, include 'Randomized treatment groups are presented' in the note. For tables using the safety population, include 'Treatment groups presented are treatment received.'

Table 14.2.2.1
Analysis of Change from Baseline in Inflammatory Lesion Count - Multiple Imputation
ITT Population

Visit	Comparison	FMX103 1.5%	Vehicle Foam
Week 12	Number of subjects	xxx	xxx
	Imputed Mean (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)
	LSM (SE)	xx.xx (xx.xx)	xx.xx (xx.xx)
	LSM 95% CI	xx.xx to xx.xx	xx.xx to xx.xx
	LSM Difference (FMX103 1.5% - Vehicle Foam) (SE)	xx.xx (xx.xx)	
	LSM Difference 95% CI	xx.xx to xx.xx	
	LSM Difference p-value	0.xxxx	
...			

Programming Note: Repeat for Week 8 and Week 4

Note: ANCOVA model includes treatment, baseline inflammatory lesion count, and analysis center. Randomized treatment groups are presented. ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; SE = standard error
Source: Listing 16.2.6.2

Table 14.2.2.2
Analysis of IGA Treatment Success - Multiple Imputation
ITT Population

Visit	Comparison	FMX103 1.5%	Vehicle Foam
Week 12	Number of subjects	xxx	xxx
	IGA Success - (%) of subjects	xx.x%	xx.x%
	Risk Ratio		
	Risk Ratio Estimate	x.xxx	
	95% Confidence Interval	x.xxx to x.xxx	
	p-value	0.xxxx	

...

Programming Note: Repeat for Week 8 and Week 4

Note: Cochran-Mantel-Haenszel test stratified by analysis center. P-value is for the null hypothesis that the combined Risk Ratio equals 1. Randomized treatment groups are presented.
Source: Listing 16.2.6.1

Table 14.2.3.1
Analysis of Change from Baseline in Inflammatory Lesion Count - LOCF
ITT Population

See Table 14.2.2.1

Note: ANCOVA model includes treatment, baseline inflammatory lesion count, and analysis center. Randomized treatment groups are presented. SE = standard error; LSM = least squares mean; CI = confidence interval
Source: Listing 16.2.6.2

Table 14.2.3.2
Analysis of Change from Baseline in Inflammatory Lesion Count - BOCF
ITT Population

See Table 14.2.2.1

Note: ANCOVA model includes treatment, baseline inflammatory lesion count, and analysis center. Randomized treatment groups are presented. SE = standard error; LSM = least squares mean; CI = confidence interval
Source: Listing 16.2.6.2

Table 14.2.3.3.x
Analysis of Change from Baseline in Inflammatory Lesion Count - Observed Cases
ITT Population

See Table 14.2.2.1 (include Weeks 4, 8, and 12)

Note: ANCOVA model includes treatment, baseline inflammatory lesion count, and analysis center. SE = standard error; LSM = least squares mean; CI = confidence interval
Source: Listing 16.2.6.2

Programming Note: Table 14.2.3.3.1 for ITT Population; Table 14.2.3.3.2 for PP Population; Remove line for imputed mean in this observed cases table. For all tables that use the ITT or PP populations, include 'Randomized treatment groups are presented' in the note. For tables using the safety population, include 'Treatment groups presented are treatment received.'

Table 14.2.3.4.x
Analysis of Percent Change from Baseline in Inflammatory Lesion Count - Observed Cases
ITT Population

See Table 14.2.2.1 (include Weeks 4, 8, and 12)

Note: ANCOVA model includes treatment, baseline inflammatory lesion count, and analysis center. SE = standard error; LSM = least squares mean; CI = confidence interval
Source: Listing 16.2.6.2

Programming Note: Table 14.2.3.4.1 for ITT Population; Table 14.2.3.4.2 for PP Population; Remove line for imputed mean in this observed cases table. For all tables that use the ITT or PP populations, include 'Randomized treatment groups are presented' in the note. For tables using the safety population, include 'Treatment groups presented are treatment received.'

Table 14.2.3.5
Analysis of Ranked Change from Baseline in Inflammatory Lesion Count - Multiple Imputation
ITT Population

Visit	Comparison [1]	FMX103 1.5%	Vehicle Foam
Week 12	Number of subjects	xxx	xxx
	Median	xx.xx	xx.xx
	Q1, Q3	xx.xx, xx.xx	xx.xx, xx.xx
	LSM Difference p-value (ranks)	0.xxxx	

Note: Q1 = first quartile or 25th percentile, Q3 = third quartile or 75th percentile. ANCOVA model includes treatment, baseline inflammatory lesion count, and analysis center.
[1] Summary statistics shown are based on observed data at Week 12. Hypothesis testing is based on multiple imputation dataset.
Source: Listing 16.2.6.2

Table 14.2.3.6
Analysis of Change from Baseline in Inflammatory Lesion Count - Analysis Center Interaction - Observed Cases (Week 12)
ITT Population

Model Effect	Overall p-value [1]
Treatment	x.xxxx
Analysis Center	x.xxxx
Treatment x Analysis Center	x.xxxx
Baseline Inflammatory Lesion Count	x.xxxx

[1] P-value for testing the statistical significance of each effect in the model. Analysis center by treatment interaction tested using a 0.10 significance level.
Source: 16.2.6.2

Table 14.2.4.1
Analysis of IGA Treatment Success - LOCF
ITT Population

See Table 14.2.2.2

Note: Cochran-Mantel-Haenszel test stratified by analysis center. P-value is for the null hypothesis that the Risk Ratio equals 1.
Source: Listing 16.2.6.1

Programming note: Add in Number of subjects with IGA treatment success before percent.

Table 14.2.4.2
Analysis of IGA Treatment Success - BOCF
ITT Population

See Table 14.2.2.2

Note: Cochran-Mantel-Haenszel test stratified by analysis center. P-value is for the null hypothesis that the Risk Ratio equals 1.
Source: Listing 16.2.6.1

Programming note: Add in Number of subjects with IGA treatment success before percent.

Table 14.2.4.3.x
Analysis of IGA Treatment Success - Observed Cases
ITT Population

See Table 14.2.2.2 (include Weeks 4, 8 and 12)

Note: Cochran-Mantel-Haenszel test stratified by analysis center. P-value is for the null hypothesis that the Risk Ratio equals 1.
Source: Listing 16.2.6.1

Programming Note: Table 14.2.4.3.1 for ITT Population; Table 14.2.4.3.2 for PP Population; For all tables that use the ITT or PP populations, include 'Randomized treatment groups are presented' in the note. For tables using the safety population, include 'Treatment groups presented are treatment received.' Programming note: Add in Number of subjects with IGA treatment success before percent.

Table 14.2.4.4
Analysis of IGA Treatment Success-Secondary - Observed Cases
ITT Population

See Table 14.2.2.2 (Week 12 data only)

Note: IGA Treatment Success-Secondary is defined as a 2-step improvement in score compared to baseline.
Cochran-Mantel-Haenszel test stratified by analysis center. P-value is for the null hypothesis that the Risk Ratio equals 1.
Source: Listing 16.2.6.1

Programming note: Add in Number of subjects with IGA treatment success before percent.

Table 14.2.5
Descriptive Summary of Subject Global Assessment
ITT Population

Visit	Category	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
Week 12	Non-missing response	xx	xx
	5-Much better than prior to treatment	xx (xx.x%)	xx (xx.x%)
	4-Slightly better than prior to treatment	xx (xx.x%)	xx (xx.x%)
	3-Same as prior to treatment	xx (xx.x%)	xx (xx.x%)
	2-Slightly worse than prior to treatment	xx (xx.x%)	xx (xx.x%)
	1-Much worse than prior to treatment	xx (xx.x%)	xx (xx.x%)
	Missing response	xx	xx

Programming Note: Continue for Week 8, Week 4, and Week 2

Note: Percentages exclude missing responses.
Source: Listing 16.2.6.4

Table 14.2.6
Descriptive Summary of Subject Satisfaction Questionnaire
ITT Population

Variable	Category	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
Rosacea Treatment	Non-missing response	xx	xx
	1-Very satisfied	xx (xx.x%)	xx (xx.x%)
	2-Satisfied	xx (xx.x%)	xx (xx.x%)
	3-Somewhat satisfied	xx (xx.x%)	xx (xx.x%)
	4-Dissatisfied	xx (xx.x%)	xx (xx.x%)
	5-Very dissatisfied	xx (xx.x%)	xx (xx.x%)
	Missing response	xx	xx
Easy to Use	Non-missing response	xx	xx
	1-Very satisfied	xx (xx.x%)	xx (xx.x%)
	2-Satisfied	xx (xx.x%)	xx (xx.x%)
	3-Somewhat satisfied	xx (xx.x%)	xx (xx.x%)
	4-Dissatisfied	xx (xx.x%)	xx (xx.x%)
	5-Very dissatisfied	xx (xx.x%)	xx (xx.x%)
	Missing response	xx	xx

Programming Note: Continue for 'Compared to Other Products', 'Feels on Skin', 'Odor', 'Color', 'Overall Satisfaction'

Recommend to Friend	Non-missing response	xx	xx
	1-Very likely	xx (xx.x%)	xx (xx.x%)
	2-Likely	xx (xx.x%)	xx (xx.x%)
	3-Somewhat likely	xx (xx.x%)	xx (xx.x%)
	4-Unlikely	xx (xx.x%)	xx (xx.x%)
	5-Very unlikely	xx (xx.x%)	xx (xx.x%)
	Missing response	xx	xx

Note: Percentages exclude missing responses. Subject Satisfaction Questionnaire is completed at the Week 12 visit or at the final visit for those subjects who prematurely withdraw from the study. Randomized treatment groups are presented.
Source: Listing 16.2.6.4

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 14.3.1.1
Summary of All Adverse Events
Safety Population

	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
All Adverse Events (AEs)	xx (xx.x%)	xx (xx.x%)
Treatment-emergent adverse events (TEAEs) [1]	xx (xx.x%)	xx (xx.x%)
Serious TEAEs (SAEs)	xx (xx.x%)	xx (xx.x%)
Treatment-related TEAEs [2]	xx (xx.x%)	xx (xx.x%)
Adverse events leading to study discontinuation	xx (xx.x%)	xx (xx.x%)
TEAEs resulting in death	xx (xx.x%)	xx (xx.x%)

Note: Percentages are 100*n/N. Number (%) of subjects with at least 1 AE in the category are presented.
Adverse events were coded using MedDRA, Version 20.0. Treatment groups are based on treatment received.
[1] For subjects who are missing the date of last dose, any AE occurring after the first dose is considered treatment emergent.
[2] Any TEAE reported as possibly related or probably related, or is missing, is considered as related to study drug.
Source: Listing 16.2.7.1

Table 14.3.1.2
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
Number of Any event	xx (xx.x%)	xx (xx.x%)
SOC 1	xx (xx.x%)	xx (xx.x%)
PT 1	xx (xx.x%)	xx (xx.x%)
PT 2	xx (xx.x%)	xx (xx.x%)
SOC 2	xx (xx.x%)	xx (xx.x%)
PT 1	xx (xx.x%)	xx (xx.x%)
PT 2	xx (xx.x%)	xx (xx.x%)
...		

Programming Note: Order SOCs by descending number of subjects (total within both treatment groups) and preferred terms within SOC also by descending number of subjects (and for all other tables where AEs are arranged by SOC and PT)

Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class and Preferred Term. Adverse events were coded using MedDRA, Version 20.0. Treatment groups are based on treatment received. For subjects who are missing the date of last dose, any AE occuring after the first dose is considered treatment emergent. AEs are sorted in descending frequency of SOC and PT.
Source: Listing 16.2.7.1

Table 14.3.1.3
Treatment-Emergent Adverse Events by Severity, System Organ Class, and Preferred Term
Safety Population

System Organ Class Preferred Term Severity	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
Any System Organ Class		
Any Event (Total)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)
Missing	xx (xx.x%)	xx (xx.x%)
SOC 1		
Any Event (Total)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)
PT 1	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)
PT 2	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)
SOC 2		
Any Event (Total)	xx (xx.x%)	xx (xx.x%)
Severe	xx (xx.x%)	xx (xx.x%)
Moderate	xx (xx.x%)	xx (xx.x%)
Mild	xx (xx.x%)	xx (xx.x%)
...		
Programming Note: Only include Missing category when SOC or PT has missing values		

Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class and Preferred Term at highest severity. Adverse events were coded using MedDRA, Version 20.0. For subjects who are missing the date of last dose, any AE occurring after the first dose is considered treatment emergent. Treatment groups are based on treatment received.
Source: Listing 16.2.7.1

Table 14.3.1.4
Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term
Safety Population

System Organ Class Preferred Term Relationship to Study Drug [1]	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
Any System Organ Class		
Any Event (Total)	xx (xx.x%)	xx (xx.x%)
Related	xx (xx.x%)	xx (xx.x%)
Not Related	xx (xx.x%)	xx (xx.x%)
SOC 1		
Any Event (Total)	xx (xx.x%)	xx (xx.x%)
Related	xx (xx.x%)	xx (xx.x%)
Not Related	xx (xx.x%)	xx (xx.x%)
PT 1	xx (xx.x%)	xx (xx.x%)
Related	xx (xx.x%)	xx (xx.x%)
Not Related	xx (xx.x%)	xx (xx.x%)
PT 2	xx (xx.x%)	xx (xx.x%)
Related	xx (xx.x%)	xx (xx.x%)
Not Related	xx (xx.x%)	xx (xx.x%)
SOC 2		
Any Event (Total)	xx (xx.x%)	xx (xx.x%)
Related	xx (xx.x%)	xx (xx.x%)
Not Related	xx (xx.x%)	xx (xx.x%)
...		

Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class and Preferred Term. Adverse events were coded using MedDRA, Version 20.0. For subjects who are missing the date of last dose, any AE occurring after the first dose is considered treatment emergent. Treatment groups are based on treatment received.
[1] Any TEAE reported as possibly related or probably related, or is missing, is considered as related to study drug unless the start date is prior to the first date of study drug administration.
Source: Listing 16.2.7.1

14.3.2 Other Serious and Significant Adverse Events

Table 14.3.2.1
Serious Adverse Events by System Organ Class and Preferred Term
Safety Population

See Table 14.3.1.2

Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class and Preferred Term. Adverse events were coded using MedDRA, Version 20.0. Treatment groups are based on treatment received.
Source: Listing 16.2.7.2

Table 14.3.2.2
Serious Adverse Events by Severity, System Organ Class, and Preferred Term
Safety Population

See Table 14.3.1.3

Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class and Preferred Term at highest severity. Adverse events were coded using MedDRA version 20.0. Treatment groups are based on treatment received.
Source: Listing 16.2.7.2

Table 14.3.2.3
Serious Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term
Safety Population

See Table 14.3.1.4

Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class and Preferred Term. Adverse events were coded using MedDRA, Version 20.0. Treatment groups are based on treatment received.
[1] Any TEAE reported as possibly related or probably related, or is missing, is considered as related to study drug unless the start date is prior to the first date of study drug administration.

Source: Listing 16.2.7.2

Table 14.3.2.4
Adverse Events Leading to Withdrawal from the Study by System Organ Class and Preferred Term
Safety Population

See Table 14.3.1.2

Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class and Preferred Term. Adverse events were coded using MedDRA, Version 20.0. Treatment groups are based on treatment received.
Source: Listing 16.2.7.3

Table 14.3.2.5
Adverse Events Leading to Withdrawal from the Study by Severity, System Organ Class, and Preferred Term
Safety Population

See Table 14.3.1.3

Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class and Preferred Term at highest severity.
Adverse events were coded using MedDRA, Version 20.0. Treatment groups are based on treatment received.
Source: Listing 16.2.7.3

Table 14.3.2.6
Adverse Events Leading to Withdrawal from the Study by Relationship to Study Drug, System Organ Class, and Preferred Term
Safety Population

See Table 14.3.1.4

Note: Percentages are 100*n/N. Subjects were counted only once for each System Organ Class and Preferred Term. Adverse events were coded using MedDRA, Version 20.0. Treatment groups are based on treatment received.
[1] Any TEAE reported as possibly related or probably related, or is missing, is considered as related to study drug unless the start date is prior to the first date of study drug administration.

Source: Listing 16.2.7.3

14.3.5 Laboratory Data Summary Tables

Table 14.3.5.1
Clinical Chemistry Results
Safety Population

Analyte	Visit	Statistic	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
Analyte 1 (unit) - Absolute value	Baseline	n (# missing)	xx (xx)	xx (xx)
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min to Max	xx.x to xx.x	xx.x to xx.x
	Week x	n (# missing)	xx (xx)	xx (xx)
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min to Max	xx.x to xx.x	xx.x to xx.x
...				
Analyte 1 (unit) - Change from baseline	Week x	n (# missing)	xx (xx)	xx (xx)
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min to Max	xx.x to xx.x	xx.x to xx.x
...				

Programming Note: Repeat for all applicable visits and all clinical chemistry analytes.

Note: Change from baseline is calculated as the value at the specified visit minus the value recorded at baseline; negative values represent a decrease in laboratory values since baseline.
Source: Listing 16.2.8.1

Table 14.3.5.2
Shift Table of Clinical Chemistry Results
Safety Population

			Assessment at Baseline				
Analyte	Treatment	Assessment at Week 12	Missing N (%)	Low N (%)	Normal N (%)	High N (%)	Total N (%)
Analyte 1 [unit]	FMX103 1.5%	Missing	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)
		Low	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)
		Normal	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)
		High	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)
		Total	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)
	Vehicle Foam	Missing	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)
		Low	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)
		Normal	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)
		High	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)
		Total	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)	xx (xxx.x%)
...							

Source: Listing 16.2.8.1

Table 14.3.5.3
Hematology Results
Safety Population

See Table 14.3.5.1

_ Note: Change from baseline is calculated as the value at the specified visit minus the value recorded at baseline; negative values represent a decrease in laboratory values since baseline.
Source: Listing 16.2.8.2

Table 14.3.5.4
Shift Table of Hematology Results
Safety Population

See Table 14.3.5.2

Source: Listing 16.2.8.2

14.3.6 Other Safety and Tolerability Summary Tables

Table 14.3.6.1
Shift Table of Physical Examination Results
Safety Population

			Assessment at Baseline				
Assessment	Treatment	Assessment at Week 12 Visit	Normal N (%)	Abnormal, NCS N (%)	Abnormal, CS N (%)	Not Done N (%)	Total N (%)
General appearence	FMX103 1.5%	Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Abnormal, NCS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Abnormal, CS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Not done	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Vehicle Foam	Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Abnormal, NCS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Abnormal, CS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Not done	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages exclude missing data. NCS = not clinically significant; CS = clinically significant
Source: Listing 16.2.9.2

Table 14.3.6.2
Vital Sign Results
Safety Population

Variable	Visit	Sample Characteristics	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
Variable1- Absolute value	Baseline	n (# missing)	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min to Max	xx.x to xx.x	xx.x to xx.x
	Week x	n (# missing)	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min to Max	xx.x to xx.x	xx.x to xx.x
...				
Variable1- Change from baseline	Week x	n (# missing)	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min to Max	xx.x to xx.x	xx.x to xx.x

Programming Note: Repeat for all vital signs variables and all scheduled visits

Note: Change from baseline is calculated as the value at the specified visit minus the value recorded at baseline; negative values represent a decrease from baseline.
Source: Listing 16.2.9.1

Table 14.3.6.3
Concomitant Medications by ATC Level 2 and Preferred Term
Safety Population

See Table 14.1.3.x

Note: Percentages are 100*n/N. Subjects were counted only once for each Anatomical Therapeutic Chemical (ATC) or preferred term. Any medications continuing or starting after Day 1 were considered to be concomitant.
[1] Medications were coded using WHO-DD (Enhanced version March 2017) ATC level 2. Preferred term is ATC level 5.
Source: Listing 16.2.9.3

Table 14.3.6.4
Summary of Local Signs and Symptoms Assessments
Safety Population

Visit	Sign/Symptom	Category	FMX103 1.5% (N=xxx)	Vehicle Foam (N=xxx)
Baseline				
	Erythema	Non-missing response	xx	xx
		0-clear skin/no signs of erythema	xx (xx.x%)	xx (xx.x%)
		1-almost clear of erythema, slight redness	xx (xx.x%)	xx (xx.x%)
		2-mild erythema, definite redness	xx (xx.x%)	xx (xx.x%)
		3-moderate erythema, marked redness	xx (xx.x%)	xx (xx.x%)
		4-severe erythema, fiery redness	xx (xx.x%)	xx (xx.x%)
		Missing response	xx	xx
	Telangiectasia	Non-missing response	xx	xx
		0-None	xx (xx.x%)	xx (xx.x%)
		1-Mild: scattered telangiectasia	xx (xx.x%)	xx (xx.x%)
		2-Moderate: numerous telangiectasia	xx (xx.x%)	xx (xx.x%)
		3-Severe: dense telangiectasia forming sprays of vessels	xx (xx.x%)	xx (xx.x%)
		Missing response	xx	xx
Programming Note: Continue for 'Burning/Stinging', 'Flushing/Blushing', 'Dryness/Xerosis', 'Itching', 'Peeling/Desquamation', 'Hyperpigmentation'				
	Hyperpigmentation	Non-missing response	xx	xx
		0-None	xx (xx.x%)	xx (xx.x%)
		1-Mild: few scattered, small areas of light hyperpigmentation	xx (xx.x%)	xx (xx.x%)
		2-Moderate: larger or more intense areas of hyperpigmentation	xx (xx.x%)	xx (xx.x%)
		3-Severe: intense, extensive hyperpigmentation	xx (xx.x%)	xx (xx.x%)
		Missing response	xx	xx
Programming Note: continue for Week 2, Week 4, Week 8, and Week 12. See protocol Section 10.7.1.1 for categories.				

Note: Percentages exclude missing responses.
Source: Listing 16.2.9.4

16.2 Subject Data Listings

16.2.1 Subject Discontinuations/Completions

Listing 16.2.1.1
Assignment to Analysis Populations and Treatment Group
All Randomized Subjects

Planned Treatment: xxxxx

Subject ID	Date of ICF	Assent Not Applicable	Date Assent Signed	Consent for Photo	Randomization		Treatment Received	Treatment Start Date	Treatment End Date	Analysis Population		
					Date	Number				SAF	ITT	PP
xxxxxx	ddmmmyyyy	xxxx	ddmmmyyyy	xxxx	ddmmmyyyy	xxxxx	xxxx	ddmmmyyyy	ddmmmyyyy	xxx	xxx	xxx
xxxxxx	ddmmmyyyy	xxxx	ddmmmyyyy	xxxx	ddmmmyyyy	xxxxx	xxxx	ddmmmyyyy	ddmmmyyyy	xxx	xxx	xxx

ICF = Informed Consent Form; SAF = Safety; ITT = Intent to Treat; PP = Per Protocol

Listing 16.2.1.2
Study Completion Status
All Randomized Subjects

Planned Treatment: xxxxx

Subject ID	Completed Study?	Discontinued From Study?	Date of Completion or Discontinuation	Reason for Discontinuation	Dose Before Completing/ Discontinuing?	AEs at Final Visit?	Date of Last Contact	Participate in FX2016-13 Study?
xxxxxx	xxxxx	xxxxx	ddmmmyyyy	xxxxx	xxxxx	xxxxx	ddmmmyyyy	no
xxxxxx	xxxxx	xxxxx	ddmmmyyyy	xxxxx	xxxxx	xxxxx	ddmmmyyyy	yes

Listing 16.2.1.3
List of Reasons for Screening Failure
Screen Failures

Subject ID	Date of ICF	Date of Screening	Date of Screen Failure	Date of Birth	Age (full years)	Sex	Race	Ethnicity	Primary Reason for Screen Failure	Failed Inclusion/ Exclusion Criteria
xxxxxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	x	xxxxx	xxxxx	xxxxx	xxxxx
xxxxxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	x	xxxxx	xxxxx	xxxxx	xxxxx

16.2.2 Protocol Deviations

Listing 16.2.2.3
Protocol Deviations
All Randomized Subjects

Planned Treatment: xxxxx

Subject ID	Date of Deviation	Severity Classification	Type	Description	Action Taken	Submitted to IRB?
xxxxxx	ddmmmyyyy	xxxxx	xxxxx	xxxxx	xxxxx	xxxxx
xxxxxx	ddmmmyyyy	xxxxx	xxxxx	xxxxx	xxxxx	xxxxx

Note: Missed doses <5 consecutive are not listed.

16.2.3 Subjects Excluded from the Efficacy Analyses

Listing 16.2.3.1
List of Subjects Excluded from Analysis Populations
All Randomized Subjects

Planned Treatment: xxxxx

Subject ID	ITT Population	PP Population	Safety Population	Reason for Exclusion from PP Population
xxxxxx	xxxxx	xxxxx	xxxxx	xxxxx
xxxxxx	xxxxx	xxxxx	xxxxx	xxxxx

Programming Note: Reason for Exclusion from PP Population will be populated from the Protocol Deviation data

16.2.4 Demographic Data and Other Baseline Characteristics

Listing 16.2.4.1
Demographic Data
All Randomized Subjects

Planned Treatment: xxxxx

Subject ID	Date of Birth	Age (full years)	Sex	Child-Bearing Potential?	Ethnicity	Race
xxxxxx	ddmmmyyyy	xx	xxxxx	xxx	xxxxx	xxxxx
xxxxxx	ddmmmyyyy	xx	xxxxx	xxx	xxxxx	xxxxx

Listing 16.2.4.2
Medical History
All Randomized Subjects

Planned Treatment: xxxxx

Subject ID	Any Medical History?	System Organ Class/ Preferred Term/ Verbatim Term	Start Date	End Date
xxxxxx	xxxxx	xxxxxxxxxxx/ xxxxxxxx/ xxxxxxxxx	ddmmmyyyy	ddmmmyyyy
xxxxxx	xxxxx	xxxxxxxxxxx/ xxxxxxxx/ xxxxxxxxx	ddmmmyyyy	Ongoing

Programming Note: If Medical Condition is Ongoing, then End Date will be "Ongoing".

Listing 16.2.4.3
Prior Medications
All Randomized Subjects

Planned Treatment: xxxxx

Subject ID	Any Medication?	Anatomic Therapeutic Class Level 2/ Preferred Term/ Verbatim Term	Start Date	End Date	Indication	Dose (unit) Route/ Frequency
xxxxxx	xxxxx	xxxxxxxxxxx/ xxxxxxxx/ xxxxxxxxx	ddmmmyyyy	ddmmmyyyy	xxxxx	xxx/ xxxxx/ xxxxxxx
xxxxxx	xxxxx	xxxxxxxxx/ xxxxxxxx/ xxxxxxxxxxx	ddmmmyyyy	Ongoing	xxxxx	xxx/ xxxxxxxxx/ xxxxxxxxx

Note: Medications were coded using WHO-DD (Enhanced version March 2017) ATC level 2. Preferred Term is ATC level 5.

Programming Note: If Medication is Ongoing, then End Date will be "Ongoing".

16.2.5 Compliance Data

Listing 16.2.5.1
Study Drug Accountability
All Randomized Subjects

Planned Treatment: xxxxx

				Dispensed					Returned			
Subject ID	Visit	Study Drug Dispensed?	Reason Not Dispensed	Date	Kit ID	Canister ID	Study Drug Returned?	Reason Not Returned	Date	Kit ID	Canister ID	Any Doses Missed?/Number
xxxxxx	xxxxx	xxx	xxxx	ddmmmyyyy	xxx	xxxx	xxx	xxxx	ddmmmyyyy	xxx	xxxx	Yes/xx
xxxxxx	xxxxx	xxx	xxxx	ddmmmyyyy	xxx	xxxx	xxx	xxxx	ddmmmyyyy	xxx	xxxx	No

Listing 16.2.5.2
Study Drug Compliance
All Randomized Subjects

Planned Treatment: xxxxx

Subject ID	First Dose Date	Last Dose Date	Treatment Duration (Days) [1]	Number of Missed Doses	Compliance (%) [2]
xxxxxx	ddmmmyyyy	ddmmmyyyy	xxx	xx	xxxx
xxxxxx	ddmmmyyyy	ddmmmyyyy	xxx	xx	xxxx

[1] Treatment duration (days) = Date of last dose of study drug - Date of first dose of study drug + 1 day.
[2] Compliance (%) = 100 x Study drug exposure (days) / Treatment duration (days).
Subjects who are missing last dose dates are not included.

Programming Note: Round compliance to one decimal.

16.2.6 Individual Efficacy Response Data

Listing 16.2.6.1
IGA Score
ITT Population

Planned Treatment: xxxxx

Analysis Center	Subject ID	Visit	Was Assessment Performed?	Reason Not Performed	Assessor Initials	Date	Study Day	IGA Score	IGA Treatment Success [1]	IGA Treatment Success - secondary [2]
xxx	xxxxxx	Screening	xxx	xxxx	xx	ddmmmyyyy	xx	x	-	-
		Baseline	xxx	xxxx	xx	ddmmmyyyy	xx	x	-	-
		Week 4	xxx	xxxx	xx	ddmmmyyyy	xx	x	xxx	xxx
		Week 8	xxx	xxxx	xx	ddmmmyyyy	xx	x	xxx	xxx
		Week 12	xxx	xxxx	xx	ddmmmyyyy	xx	x	xxx	xxx
xxx	xxxxxx	Screening	xxx	xxxx	xx	ddmmmyyyy	xx	x	xxx	xxx

[1] IGA treatment success is Yes if the IGA score is either 0 or 1 and there is at least a 2-grade improvement (decrease) from baseline. Otherwise IGA treatment success is No.
[2] IGA treatment success - secondary is Yes if there is at least a 2-grade improvement (decrease) from baseline. Otherwise IGA treatment success - secondary is No.

Listing 16.2.6.2
Inflammatory Lesion Count by Facial Area
ITT Population

Planned Treatment: xxxxx

Analysis Center	Subject ID	Visit	Assessor Initials	Date	Study Day	Facial Area	Facial Area Not Assessed?	Reason Not Assessed	Papules	Pustules	Nodules	Total
xxx	xxxxxx	Screening	xx	ddmmmyyyy	xx	Forehead	xxx	xxxxx	xx	xx	xx	xx
						Right cheek	xxx	xxxxx	xx	xx	xx	xx
						Left cheek	xxx	xxxxx	xx	xx	xx	xx
						Nose	xxx	xxxxx	xx	xx	xx	xx
						Chin	xxx	xxxxx	xx	xx	xx	xx
						Total			xx	xx	xx	xx
		Baseline	xx	ddmmmyyyy	xx	Forehead	xxx	xxxxx	xx	xx	xx	xx
		Week 4	xx	ddmmmyyyy	xx	Forehead	xxx	xxxxx	xx	xx	xx	xx
		Week 8	xx	ddmmmyyyy	xx	Forehead	xxx	xxxxx	xx	xx	xx	xx
		Week 12	xx	ddmmmyyyy	xx	Forehead	xxx	xxxxx	xx	xx	xx	xx
xxx	xxxxxx	Screening	xx	ddmmmyyyy	xx	Left cheek	xxx	xxxxx	xx	xx	xx	xx

Listing 16.2.6.3
Subject Satisfaction Questionnaire (SSQ)
ITT Population

Planned Treatment: xxxxx

Subject ID	Date	Study Day	Question	Response
xxxxxx	ddmmmyyyy	xx	How satisfied are you with this product in treating your rosacea?	xxxxx
			How satisfied are you with how easy this product is to use?	xxxxx
			How satisfied are you with this product compared to other products you have previously used for rosacea, such as gels and creams?	xxxxx
			How satisfied are you with how this product feels on you skin after treatment?	xxxxx
			How satisfied are you with the odor of this product after treatment?	xxxxx
			How satisfied are you with the color of this product after treatment?	xxxxx
			Overall, how satisfied are you with this product?	xxxxx
			Overall, how likely are you to recommend this product to a friend?	xxxxx
xxxxxx	ddmmmyyyy	xx	How satisfied are you with this product in treating your rosacea?	xxxxx

Listing 16.2.6.4
Subject Global Assessment (SGA)
ITT Population

Planned Treatment: xxxxx

Subject ID	Date	Study Day	Visit	Response
xxxxxx	ddmmmyyyy	xx	Week 2	xxxxx
			Week 4	xxxxx
			Week 8	xxxxx
			Week 12	xxxxx
xxxxxx	ddmmmyyyy	xx	xxxxx	xxxxx

16.2.7 Adverse Event Listings

Listing 16.2.7.1
Adverse Events
Safety Population

Subj ID	Any AEs?	TEAE?	System Organ Class/ Preferred Term/ Verbatim Term	Start Date	End Date	Severity/ Rel to Study Drug	Outcome/ Study Drug Action Taken	Serious?/ Life-Threat?	Hosp	Disab	Birth Defect?	Med Sig?
xxxxxx	xxx	xx	xxxxx/ xxxxxxx/ xxxxxxxxx	ddmmmyyyy	ddmmmyyyy	xxxx/ xxxxxx	xxxx/ xxxxxxxx	xx/ xx	xx	xxx	xxx	xx
xxxxxx	xxx	xxx	xxxxx/ xxxxxxx/ xxxxxxxxx	ddmmmyyyy	Ongoing	xxxx/ xxxxxx	xxxx/ xxxxxxx	xx/ xx	xx	xx	xx	xx

Note: Adverse events were coded using MedDRA, Version 20.0. Rel = Relationship; Threat = Threatening; Hosp = Requires Inpatient/Prolonged Hospitalization; Disab = Results in Persistent or Significant Disability or Incapacity; Birth Defect = Congenital Anomaly or Birth Defect; Med Sig = Medically Significant; Trtmnt Req = Treatment Required

Programming Note: If AE is Ongoing then report 'Ongoing' for 'End Date'

Listing 16.2.7.2
Serious Adverse Events
Safety Population

Treatment Received: xxxxx

See Listing 16.2.7.1; Remove ‘Any AEs?’ column

Listing 16.2.7.3
Adverse Events Leading to Withdrawal
Safety Population

Treatment Received: xxxxx

See Listing 16.2.7.1; Remove ‘Any AEs?’ column

Listing 16.2.7.4
Deaths
Safety Population

Treatment Received: xxxxx

See Listing 16.2.7.1; Remove ‘Any AEs?’ column

16.2.8 Laboratory Values

Listing 16.2.8.1
Clinical Chemistry Results
Safety Population

Treatment Received: xxxxx

Subject ID	Lab Test (unit)	Visit	Samples Collected?	Reason Not Collected	Collection Date	Result	Reference Range Low	Reference Range High	Abnormal?	Clinically Significant?
xxxxxx	xxxxx	xxxxx	xxxx	xxxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxxx	xxxx
		xxxxx	xxxx	xxxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxxx	xxxx

Listing 16.2.8.2
Hematology Results
Safety Population

Treatment Received: xxxxx

Subject ID	Lab Test (unit)	Visit	Samples Collected?	Reason Not Collected	Collection Date	Result	Reference Range Low	Reference Range High	Abnormal?	Clinically Significant?
xxxxxx	xxxxx	xxxxx	xxxx	xxxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxxx	xxxx
		xxxxx	xxxx	xxxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxxx	xxxx

Listing 16.2.8.3
Urinalysis Results
Safety Population

Treatment Received: xxxxx

Subject ID	Lab Test (unit)	Visit	Samples collected?	Reason Not Collected	Collection Date	Result	Reference Range Low	Reference Range High	Abnormal?	Clinically Significant?
xxxxxx	xxxxx	xxxxx	xxxx	xxxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxxx	xxxx
		xxxxx	xxxx	xxxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxxx	xxxx

Listing 16.2.8.4
Clinically Significant Laboratory Tests for Hematology, Chemistry, and Urinalysis
All Randomized Subjects

Treatment Received: xxxxx

Subject ID	Visit	Category	Lab Test (unit)	Collection Date	Result	Reference Range Low	Reference Range High	Abnormal?
xxxxxx	xxxxx	xxxx	xxxxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxxx
	xxxxx	xxxx	xxxxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxxx

Programming Note: Include pre-treatment portion for 'Not Treated' group, variable Abnormal should be high or low

Listing 16.2.8.5
Out of Range (Abnormal) Laboratory Tests for Hematology, Chemistry, and Urinalysis
All Randomized Subjects

Treatment Received: xxxxx

Subject ID	Visit	Category	Lab Test (unit)	Collection Date	Result	Reference Range Low	Reference Range High	Abnormal?	Clinically Significant?
xxxxxx	xxxxx	xxxx	xxxxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxxx	xxxx
	xxxxx	xxxx	xxxxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxxx	xxxx

Programming Note: Include pre-treatment portion for 'Not Treated' group

Listing 16.2.8.6
Pregnancy Test Results
Safety Population

Treatment Received: xxxxx

Subject ID	Visit	Pregnancy Test Performed?	Reason Not Performed	Collection Date	Result
xxxxxx	xxxxx	xxxx	xxxx	ddmmmyyyy	xxxxx
	xxxxx	xxxx	xxxx	ddmmmyyyy	xxxxx

16.2.9 Other Clinical Observations and Measurements

Listing 16.2.9.1
Vital Signs
Safety Population

Treatment Received: xxxxx

Subject ID	Visit	Vital Signs Collected?	Collection Date	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)	Heart Rate (beats/min)	Systolic BP (mmHg)	Diastolic BP (mmHg)
xxxxxx	xxxxx	xxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxx	xxx	xxx
	xxxxx	xxx	ddmmmyyyy	xxxx	xxxx	xxxx	xxx	xxx	xxx

Listing 16.2.9.2
Abnormal Physical Examination Results
Safety Population

Treatment Received: xxxxx

Subject ID	Visit	Examination Date	Body System	Result	Abnormal Finding
xxxxxx	xxxxx	ddmmmyyyy	xxxx	xxxx	xxxx
			xxxx	xxxx	xxxx

Listing 16.2.9.3
Concomitant Medications
Safety Population

Treatment Received: xxxxx

See Listing 16.2.4.3

Programming Note: If Medication is Ongoing, then End Date will be "Ongoing".

Listing 16.2.9.4
Local Signs and Symptoms Assessments
Safety Population

Treatment Received: xxxxx

Subject ID	Date	Assessment Performed?	Study Day	Assessor Initials	Sign/Symptom	Severity [1]
xxxxxx	ddmmmyyyy	xxxxx	xxxxx	xxxxx	Erythema	xxxx
					Telangiectasia	xxxx
					Burning/Stinging	xxxx
					Flushing/Blushing	xxxx
					Dryness/Xerosis	xxxx
					Itching	xxxx
					Peeling/Desquamation	xxxx
					Hyperpigmentation	xxxx
xxxxxx	ddmmmyyyy	xxxxx	xxxxx	xxxxx	Erythema	xxxx

[1] All signs/symptoms, except erythema, are based on a 4-point scale with 0=none, 1=mild, 2=moderate, and 3=severe. Erythema is based on a 5-point scale with 0=clear, 1=almost clear, 2=mild erythema, 3=moderate erythema, and 4=severe erythema.

Listing 16.2.9.5
Photography of the Face
Safety Population

Treatment Received: xxxxx

Subject ID	Visit	Photography Performed?	Photography Date	Photography Study Day
xxxxxx	Baseline	xxxxx	ddmmmyyyy	xxx
	Week 4	xxxxx	ddmmmyyyy	xxx
	Week 8	xxxxx	ddmmmyyyy	xxx
	Week 12	xxxxx	ddmmmyyyy	xxx
xxxxxx	xxxxx	xxxxx	ddmmmyyyy	xxx