A Randomized, Double-Blind, Vehicle-Controlled Study to evaluate the Efficacy and Safety of Topical Administration of FMX101 for 12 Weeks in the Treatment of Moderate-to-Severe Acne Vulgaris (Study FX2017-22)

Statistical Analysis Plan

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Foamix Pharmaceuticals Inc.'s protocol number FX2017-22 (A Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Efficacy and Safety of Topical Administration of FMX101 for 12 Weeks in the Treatment of Moderate-to-Severe Acne Vulgaris), Version 1 dated 22 June 2017. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to 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 Foamix Pharmaceuticals Inc.'s study FX2017-22.

2. Study Objectives and Endpoints

2.1. Study Objectives

The objectives of this study are:

- To evaluate the efficacy in the treatment of acne compared to vehicle of topical FMX101 4% administered daily for 12 weeks.
- To evaluate the safety compared to vehicle of topical FMX101 4% administered 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), any treatment-emergent AEs (TEAEs), any serious TEAE (SAE), any treatment-related TEAE, any TEAE leading to study discontinuation
- Changes from baseline in vital signs, laboratory parameters, and physical examinations
- Assessment of tolerability, in particular erythema, dryness, hyperpigmentation, skin peeling, and itching at the sites of study drug application

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 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 or 1, and at least a 2-grade improvement (decrease) from Baseline

2.2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

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

2.2.2.3. Tertiary Efficacy Endpoints

The tertiary efficacy endpoints of this study include the following:

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

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 over 12 weeks of FMX101 topical foam containing 4% minocycline compared to vehicle in the treatment of subjects with moderate-to-severe facial acne vulgaris. Subjects with qualifying lesion counts and IGA of acne severity scores will be enrolled and randomly assigned in a 1:1 ratio (active:vehicle) to receive 1 of the following 2 treatments:

- FMX101 4% 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 subject will be blinded to the study drug identity.

Subjects will return for visits at Weeks 1, 3, 6, 9, and 12. At the discretion of the clinic staff 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 1, 3, and 6 visits and 7 days before or after for the Weeks 9 and 12 visits. Efficacy evaluations (acne lesion counts and IGA) will be performed at Screening/Baseline and at Weeks 3, 6, 9, and 12 during the study.

All enrolled subjects will be included in the study with the exception of data collected from Study Center 374 which will be excluded from all listings, tables and analyses due to the significant quality issues identified during the conduct of the study. The corresponding monitoring and quality assurance audit reports for this center will be held within the study trial master file (TMF).

3.2. Sample Size and Power

In a pooled analysis of 2 Phase 3 studies of FMX101 4% in subjects with acne (Studies FX2014-04 and FX2014-05), the proportion of subjects with an IGA score of 0 or 1 after 12 weeks of treatment was 11.51% in the FMX101 4% group compared to 6.34% in the vehicle group (p=0.0188). Table 5 in the protocol provides a few alternate assumptions and corresponding sample sizes. Power was set to 90% and type-1 error to 2-sided 0.05. Sample size was calculated based on Fisher's exact test.

Assuming a 13% dropout rate and a 1:1 randomization, 750 subjects receiving active and 750 subjects receiving vehicle will provide at least 90% power to demonstrate a statistically significant difference between the treatment arms.

Also in Studies FX2014-04 and FX2014-05, the change from baseline in inflammatory lesions in the minocycline 4% foam groups (-14.16 and -13.46, respectively) vs. the vehicle groups (-11.17 and -10.72, respectively) were highly statistically significant in total populations of under 500 subjects.

A pooled analysis of the change from baseline in non-inflammatory lesions from Studies FX2014-04 and FX2014-05 indicates that 1500 subjects will be sufficient to show numerical and statistical superiority of FMX101 4% compared to vehicle.

In summary, 750 subjects receiving active treatment and 750 receiving vehicle will provide >90% power for a statistically significant difference in IGA response and is sufficiently large enough to show a statistically significant difference in effects on inflammatory lesions and non-inflammatory lesions.

3.3. Study Population

The study population comprises healthy male and non-pregnant females, aged ≥9 years, with a clinical diagnosis of moderate-to-severe facial acne vulgaris.

3.4. Treatments Administered

This is a double-blind study with 1:1 randomization between FMX101 4% and vehicle foam. FMX101 4% 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 randomized to treatment using the interactive response technology (IRT) system.

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

If unblinding is necessary, the subject will be withdrawn from the study and Early Termination (ET) Visit (ie, Visit 6 [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[a]	Baseline[a]	Visits				Final Visit[b]
Visit		1	2	3	4	5	6
Week			1	3	6	9	12
Informed Consent/Assent	X						
Demographic data	X						
Assign identification number	X						
Medical/Surgical/Medication (prior/concomitant) history	X						
Inclusion/Exclusion criteria	X	X					
Physical examination, height, weight[c]		X					X
Blood pressure/heart rate[d]		X	X	X	X	X	X
Blood and urine samples for clinical laboratory tests	X			X			X
Urine pregnancy test (females of childbearing potential only)		X		X	X	X	X
Investigator's Global Assessment[e]	X	X		X	X	X	X
Lesion counts[e]	X	X		X	X	X	X
Photography[f]		X					X
Subject Satisfaction Questionnaire							X
Randomization		X					
Concomitant medications		X	X	X	X	X	X
Adverse events		X	X	X	X	X	X
Tolerability assessments			X	X	X	X	X
Perform drug accountability			X	X	X	X	X
Collect used drug canister(s)			X	X	X	X	X
Dispense study drug		X		X	X	X	
Schedule/confirm next visit	X	X	X	X	X	X	

a. The duration of Screening is variable but if there are medications to be discontinued it cannot be less than the time indicated in Exclusion Criterion 9. The procedures required at Screening/Baseline can be combined. **However, study drug should not be dispensed until all inclusion and exclusion criteria are met.**

b. If a subject prematurely withdraws from the study, all evaluations described under Visit 6/Week 12 (Final Visit) must be performed at an Early Termination Visit.

c. Height to be measured only at Baseline.

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

e. **Every attempt must be made to ensure the same evaluator performs the efficacy evaluations for a particular subject throughout the study.**

f. Only for study centers participating in subject photography.

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, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or 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.
- **Intent-To-Treat Population (ITT):** The ITT Population includes all randomized subjects.
- **Per-Protocol (PP)**: The PP Population is defined as the subset of the ITT population without any protocol deviations that may impact on the efficacy assessments. 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 FX2017-22 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 administered any interfering concomitant medications
- Have not, in the opinion of the investigator, been compliant with the treatment regimen (eg, reported frequent missed doses)
- Randomization error

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

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

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

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 and baseline non-inflammatory lesion count will be included as a covariate, respectively, in the ANCOVA for the change in inflammatory lesion count and change in non-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 (with the exception of the non-inflammatory lesion count endpoint) 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)

MI will be the imputation method 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 3, 6, 9, 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 above 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 3, 6, 9, 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 predictive mean matching[8] method for monotone data with a donor pool of 5 closest predicted observations 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 in order to normalize prior to combining. The estimated $\log(Risk\ Ratio)$ and corresponding 95% confidence interval will be back transformed from the combined results.

A pre-specified seed number of 458936251 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 also 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 1 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 1	7	Post-dose — Day 14
3	Week 3	21	15 — 31
4	Week 6	42	32 — 52
5	Week 9	63	53 — 73
6	Week 12	84	74 — 94

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 12 subjects assigned to each treatment 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)

- Total number of non-inflammatory lesion count = number of open comedones + number of closed comedones in all facial areas (forehead, left and right cheeks, nose, and chin)

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

  Thus, a positive change will reflect a reduction in lesion count. Change from baseline will be calculated at the following time points: 3, 6, 9, and 12 weeks.

- Percentage change from baseline lesion count = $100 \times \frac{value\ at\ baseline - post\ baseline\ value}{value\ at\ baseline}$

  Thus, a positive percentage change will reflect a reduction in lesion count. The percentage change from baseline will be calculated at the following time points: 3, 6, 9, and 12 weeks.

- TEAE = any adverse event with an onset date on or after the first application of study drug, and before to the last application of study drug plus 3 days, having been absent pre-treatment or worsening relative to the pre-treatment state.

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

- Age groups Age group = 1 if $9 \leq$ age (full years) ≤ 12
  Age group = 2 if $13 \leq$ age (full years) ≤ 17
  Age group = 3 if $18 \geq$ 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 those 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 that were dispensed incorrect kits with inconsistent treatment regimen. Date of study drug application is assumed to be the date of dispensation.

- 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

6.1.9. Data Adjustments/Handling/Conventions

All collected data will be presented in listings with the exception of data collected from Study Center 374 which will be excluded from all listings, tables and analyses due to the significant quality issues identified during the conduct of the study. The corresponding monitoring and quality assurance audit reports for this center will be held within the study trial master file (TMF).

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.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. In general, TEAEs are defined as AEs 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 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 adverse event that started before the first dose 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.

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

Adverse events or medications with entirely missing 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 study drug value will be considered 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 "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 reflect the date of onset of an adverse event, 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 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, 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 (9 to 12 years , 13 to 17, ≥ 18 years)
- Sex
- Race
- Ethnicity
- Baseline body weight (kg), height (cm), and BMI (kg/m^2)
- Baseline lesion count (inflammatory, non-inflammatory)
- 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 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 FMX101 4% to be 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 FMX101 4% and vehicle are:

- 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[7]. The combined estimated mean difference in change from baseline (FMX101 4% 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 FMX101 4% vs. vehicle foam, and associated 95% confidence limits will be back-transformed. The combined Mantel-Haenszel risk ratio, along with its estimated 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 and Tertiary Efficacy Analysis

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

- absolute and percentage change from baseline in inflammatory lesion count
- absolute and percentage change from baseline in non-inflammatory lesion count
- IGA success rate

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

Secondary and tertiary 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. Exploratory Efficacy Analysis

Further investigation of the efficacy data will be conducted similarly to the appropriate co-primary efficacy parameter for the following endpoints:

- Absolute change from baseline in inflammatory lesion count and IGA Treatment Success at Week 12 for subjects aged ≥ 18 years
- Absolute change from baseline in inflammatory lesion count and IGA Treatment Success at Week 12 for subjects aged < 18 years

The exploratory efficacy analyses will be based on the ITT Population using MI.

8.4. Subject Satisfaction Questionnaire

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

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 skin tolerability.

All safety analyses will be performed on the Safety Population. Subjects will be reported according to the treatment they actually received. Subjects who were inadvertently administered incorrect kits and were exposed to the wrong treatment for ≥ 20% of their treatment duration will be included in the FMX101 4% group for all safety assessments. Subjects who were exposed to the wrong treatment 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 based on descriptive statistics by treatment group and 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.

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 conservatively summarized as severe. Through the data cleaning process, all attempts will be made to avoid missing values for relationship and severity.

All TEAEs summarized by system organ class (SOC) and preferred term (PT) will be 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. The summary will include the total number of events, frequency counts and percentages with:

- Any AEs
- Any TEAEs
- Any SAEs
- Any treatment-related TEAE
- 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

In the case of 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 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

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and PT will be prepared 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 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. 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 by time point will be tabulated for each clinical laboratory analyte. 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 is based on the Investigator's judgment.

Urinalysis test results 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, body weight, height, and BMI. BMI and height will be presented at baseline only.

9.4. Physical Examinations

Physical examinations will be summarized using descriptive statistics at Baseline and at 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 Skin Tolerability

Erythema, dryness, hyperpigmentation, and skin peeling at the sites of study drug application will be assessed at each study visit on a scale of 0 to 3 (0=none; 1=mild; 2=moderate; 3=severe).

Itching will be assessed using the same scale based on the subjects' subjective assessment. The intensity and location of each finding will be recorded.

The severity of erythema, dryness, hyperpigmentation, skin peeling, and itching will be summarized using frequency counts and percentages at each visit by treatment group.

9.6. Prior and Concomitant Medication

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).

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 exclusion of study subject data collected from site 374 due to significant quality issues identified during the conduct of the study.

An exploratory efficacy analysis of the co-primary endpoints by age group has been added.

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. Rubin, D.B (1987). Multiple Imputation for Nonresponse in Surveys. New York. John Wiley & Sons.
8. Little, R.J.A. (1988). A Test of Missing Completely at Random for Multivariate Data with Missing Values, Journal of the American Statistical Association, 83, 404, 1198-1202.

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 number FX2017-22. 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 16.2.6.3
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 Non-inflammatory Lesion Count	16.2.6.3
Table 14.2.1.3	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 Change from Baseline in Inflammatory Lesion Count by Age - Multiple Imputation	16.2.6.2
Table 14.2.3.6	ITT	Analysis of Ranked Change from Baseline in Inflammatory Lesion Count - Multiple Imputation	16.2.6.2
Table 14.2.3.7	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 by Age - Multiple Imputation	16.2.6.1

Table Number	Population(s)	Table Title / Summary	Supporting listing
Table 14.2.5	ITT, PP	Analysis of Change from Baseline in Non-Inflammatory Lesion Count - Observed Cases	16.2.6.3
Table 14.2.6	ITT, PP	Analysis of Percent Change from Baseline in Non-Inflammatory Lesion Count - Observed Cases	16.2.6.3
Table 14.2.7	ITT	Descriptive Summary of Subject Satisfaction Questionnaire	16.2.6.4

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 Table 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 Skin Tolerability Assessment	16.2.9.4

14.1. Planned Listing Descriptions

The following are planned data and subject data listings for protocol number FX2017-22.

In general, one listing will be produced per CRF domain.

All listings will be sorted by treatment, analysis center, site, and subject number.

All calculated variables will be included in the listings.

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	Major 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	Non-inflammatory Lesion Count by Facial Area
Data listing 16.2.6.4	ITT	Subject Satisfaction Questionnaire (SSQ)
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 Skin Tolerability Assessment (LSTA)
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 Listing 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
SOC	system organ class
TEAE	treatment-emergent adverse event
TMF	trial master file