# Integrated Safety and Efficacy Analysis of FMX103 1.5% Topical Minocycline Foam for the Treatment of Moderate-to-Severe Papulopustular Rosacea: Results From Two Phase 3 Studies

James Q. Del Rosso, DO[1]; Linda Stein Gold, MD[2]; Leon Kircik, MD[3]; Neal D. Bhatia, MD[4]; Neil Sadick, MD[5]; Matthew Zirwas, MD[6]; Edward Lain, MD[7]; Iain Stuart, PhD[8]

[1]JDR Dermatology Research/Thomas Dermatology, Las Vegas, NV; [2] Henry Ford Health System, Detroit, MI; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]Therapeutics Clinical Research, San Diego, CA; [5]Sadick Dermatology, New York, NY; [6]Dermatologists of the Central States, Columbus, OH; [7]Sanova Dermatology, Austin, TX; [8]Menlo Therapeutics Inc., Bridgewater, NJ

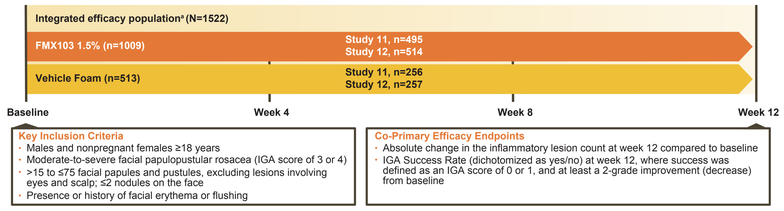
## Introduction

- Rosacea is a common, chronic, inflammatory cutaneous disorder involving the face that affects approximately 16 million individuals in the United States[1,2]
- Rosacea is typically characterized by cutaneous signs such as flushing, erythema, edema, papules, and pustules[1-5]
- Topical therapies such as metronidazole, azelaic acid, and ivermectin are considered first-line therapies for papulopustular rosacea[2-5]
  - Oral tetracyclines, specifically doxycycline and minocycline, are mainstays of treatment for moderate-to-severe disease; however, they have the potential for significant systemic side effects[2,4]
  - Independent of their antimicrobial activity, tetracyclines may exert beneficial effects in rosacea due, in part, to their anti-inflammatory, antiapoptotic, and antiangiogenic activities[6]
- FMX103 1.5% is a topical minocycline foam being developed for the treatment of moderate-to-severe papulopustular rosacea[7,8]
  - The efficacy, safety, and tolerability of FMX103 1.5% from two identical, Phase 3, randomized, double-blind, vehicle-controlled studies, FX2016-11 (Study 11) and FX2016-12 (Study 12), have previously been presented[8]
- **Objective:** To compare integrated efficacy and safety of FMX103 1.5% vs vehicle administered daily for 12 weeks

## Methods

- The 2 pivotal Phase 3 studies (FX2016-11, Study 11; FX2016-12, Study 12) were randomized, double-blind comparisons of FMX103 1.5% with vehicle foam **(Figure 1)**
- Qualified subjects were enrolled and randomly assigned in a 2:1 ratio to receive either FMX103 1.5% or vehicle
- Subjects applied the assigned study drug once daily for 12 weeks and returned for visits at Weeks 2, 4, 8, and 12
- The efficacy data from Studies 11 and 12 were pooled for analysis both in totality and for the predefined subgroup of baseline disease severity (moderate, IGA=3; severe, IGA=4)
- Safety endpoints included adverse events and local facial tolerability assessments, which were summarized for the overall pooled population, as well as for predefined subgroups including sex, race, age, and baseline disease severity

### Figure 1. Study design




[a]The integrated efficacy population consisted of all randomized subjects that were pooled from Studies 11 (n=751) and 12 (n=771). One subject was randomized but discontinued prior to taking the first dose and was therefore not included in the integrated safety population.
IGA, Investigator's Global Assessment; based upon a 5-point scale with 0=clear, 1=almost clear, 2=mild, 3=moderate, and 4=severe.

## Results

### Baseline Demographics and Disease Characteristics

- 1522 subjects were included in the integrated efficacy population
- Baseline demographics and disease characteristics are shown in **Table 1**
- The majority of subjects were female (70.6%) and white (96.4%). The mean age was 50.0 and ranged from 18-86 years. At baseline, 86.9% and 13.1% of subjects had moderate (IGA=3) or severe (IGA=4) disease, respectively
- Baseline demographics and disease characteristics were similar across treatment groups

### Table 1. Baseline demographics and disease characteristics

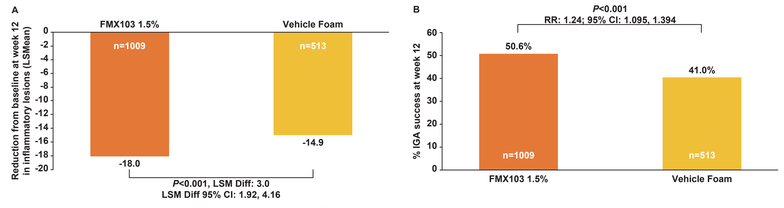
| Variable | FMX103 1.5% (n=1009) | Vehicle Foam (n=513) | Overall (N=1522) |
|---|---|---|---|
| Mean age (SD) | 49.9 (13.84) | 50.3 (13.17) | 50 (13.61) |
| 18 to 40 years, n (%) | 265 (26.3) | 118 (23.0) | 383 (25.2) |
| 41 to 64 years, n (%) | 588 (58.3) | 311 (60.6) | 899 (59.1) |
| 65 years, n (%) | 156 (15.5) | 84 (16.4) | 240 (15.8) |
| Sex, m (%) | | | |
| Male | 289 (28.6) | 159 (31.0) | 448 (29.4) |
| Female | 720 (71.4) | 354 (69.0) | 1074 (70.6) |
| Race | | | |
| White | 973 (96.5) | 491 (96.1) | 1464 (96.4) |
| Black | 14 (1.4) | 5 (1.0) | 19 (1.3) |
| Other | 21 (2.1) | 15 (2.9) | 36 (2.4) |
| Mean inflammatory lesion count, n (SD) | 29.2 (12.48) | 29.6 (12.57) | 29.4 (12.5) |
| IGA score, n (%) | | | |
| 3 – Moderate | 887 (87.9) | 435 (84.8) | 1322 (86.9) |
| 4 – Severe | 122 (12.1) | 78 (15.2) | 200 (13.1) |

IGA, Investigator's Global Assessment; SD, standard deviation.
Note that percentages exclude missing values.

### Pooled Efficacy Data

- In the combined analysis of the two pivotal Phase 3 studies, FMX103 1.5% demonstrated statistically significant benefit compared to vehicle foam for both co-primary endpoints **(Figure 2)**
  - At week 12, FMX103 1.5% demonstrated a significantly greater reduction from baseline in inflammatory lesions than vehicle foam **(Figure 2A)**
  - A significantly greater number of subjects receiving FMX103 1.5% achieved IGA treatment success at week 12 than those receiving vehicle foam **(Figure 2B)**

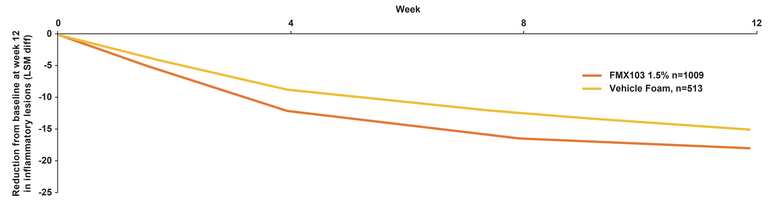
### Figure 2. Co-primary efficacy endpoints




IGA, Investigator's Global Assessment; LSM Diff, LSMean Difference; CI, Confidence Interval; RR, risk ratio.
Integrated efficacy population (multiple imputation).

- FMX103 1.5% demonstrated a statistically significant advantage over vehicle foam for inflammatory lesions beginning as early as week 4 **(Figure 3)**
  - The FMX103 1.5% group exhibited a significantly greater reduction in inflammatory lesions at week 4 than the vehicle foam group
  - This statistically significant advantage over vehicle was maintained at weeks 8 and 12

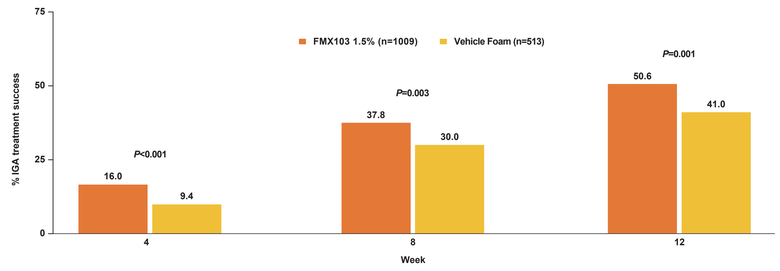
### Figure 3. Change from baseline in inflammatory lesion counts by visit




Integrated efficacy population (multiple imputation); LSM diff, least squares mean difference

- FMX103 1.5% demonstrated a statistically significant advantage over vehicle foam for IGA treatment success beginning as early as week 4 **(Figure 4)**
  - This statistical advantage over vehicle was maintained throughout the study, with approximately half of the subjects in the FMX103 1.5% group achieving treatment success by week 12

### Figure 4. IGA treatment success over time

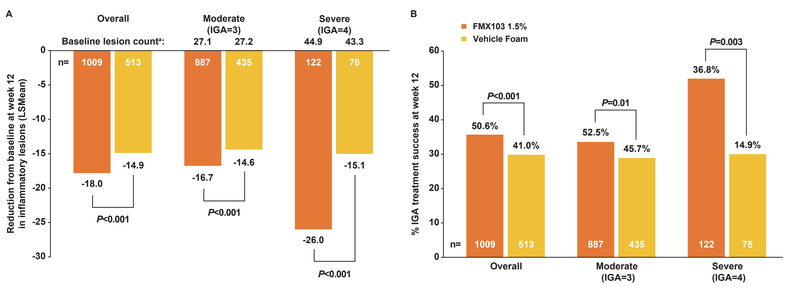



IGA, Investigator's Global Assessment; Integrated efficacy population (multiple imputation); P values are based on common risk ratios.

### Efficacy Results In The Patient Subgroups Scored As Moderate Or Severe At Baseline

- FMX103 1.5% demonstrated statistically significant advantages over vehicle foam in both baseline disease severity subgroups **(Figure 5)**
  - In both moderate (IGA=3) and severe (IGA=4) subpopulations, the change from baseline at week 12 in inflammatory lesions was significantly greater in the FMX103 1.5% group than in the vehicle foam group **(Figure 5A)**
  - Similarly, a significantly greater number of subjects in the FMX103 1.5% group achieved IGA treatment success by week 12 than in the vehicle foam group, regardless of baseline disease severity **(Figure 5B)**
  - The treatment effect for FMX103 1.5% vs vehicle foam was more pronounced in the severe subgroup than in the moderate subgroup for both inflammatory lesions **(Figure 5A)** and IGA treatment success **(Figure 5B)**

### Figure 5. Efficacy of FMX103 1.5% across baseline disease severities




IGA, Investigator's Global Assessment; Integrated efficacy population (multiple imputation); [a]Baseline lesion counts are based on observed cases.

### Safety Endpoints

- Overall summary of Adverse Events is shown in **Table 2**
- All serious TEAEs were considered by the investigators as not related to study drug
- 9 subjects reported 10 TEAEs resulting in study discontinuation
  - 7 subjects in the FMX103 1.5% group and 2 subjects in the vehicle group
  - One TEAE (moderate pruritis) leading to drug withdrawal was considered related to study drug. The subject was randomized to FMX103 1.5% treatment

### Table 2. Summary of TEAEs and AEs in the integrated safety population

| | FMX103 1.5% (n=1008) | Vehicle Foam (n=513) | Overall (N=1521) |
|---|---|---|---|
| Subjects with any AE, n(%) | 232 (23) | 129 (25.1) | 361 (23.7) |
| Number of AEs | 380 | 200 | 580 |
| Subjects with any TEAE, n(%) | 219 (21.7) | 122 (23.8) | 341 (22.4) |
| Number of TEAEs | 350 | 184 | 534 |
| Subjects with any serious TEAE, n(%) | 3 (0.3) | 5 (1.0) | 8 (0.5) |
| Number of serious TEAEs | 8[a] | 9[b] | 17 |
| Subjects with any treatment-related TEAE, n(%) | 3 (0.3) | 5 (1.0) | 8 (0.5) |
| Number of treatment-related TEAEs | 24[c] | 17[d] | 41 |
| Subjects with any TEAE leading to discontinuation, n(%) | 7 (0.7) | 2 (0.4) | 9 (0.6) |
| Number of TEAEs leading to study discontinuation | 8[e] | 2[f] | 10 |

[a]Nausea, chest discomfort, fatigue, seasonal allergy, dehydration, syncope, dyspnea, hypertension
[b]Gastrointestinal hemorrhage, chest pain, pyrexia, dyspnea, asthma, hypertension, myocardial infarction, tachycardia
[c]Pruritis, rash, dermatitis, dermatitis contact, hair color changes, nail discoloration, skin hyperpigmentation, application site pain, application site erythema, facial pain, nodule, migraine, dizziness, dysgeusia, aphthous ulcer, cheilitis, eye irritation, ophthalmic herpes simplex, sunburn
[d]Nail discoloration, rosacea, skin exfoliation, application site pain, facial pain, application site pruritis, headache, cellulitis, skin cancer, urine odor abnormal
[e]Pruritis, dermal cyst, dermatitis, telangiectasia, influenza, urinary tract infection, bladder mass
[f]Rash pustular, myocardial infarction

- The incidence rate of the most frequently reported TEAEs (≥1% in any group) was similar between treatment groups **(Table 3)**
- Overall, most subjects reported TEAEs that were not related to study drug (89.7%, 306/341)

### Table 3. Summary of non-cutaneous TEAEs in the integrated safety population by preferred term (≥1% in any group)

| TEAEs in ≥1% of subjects in either group, n (%) | FMX103 1.5% (n=1008) | Vehicle Foam (n=513) | Overall (N=1521) |
|---|---|---|---|
| Viral upper respiratory tract infection | 24 (2.4) | 12 (2.3) | 36 (2.4) |
| Upper respiratory tract infection | 19 (1.9) | 13 (2.5) | 32 (2.1) |
| Headache | 14 (1.4) | 10 (1.9)[a] | 24 (1.6) |
| Sinusitis | 11 (1.1) | 2 (0.4) | 13 (0.9) |
| Diarrhea | 10 (1.0) | 2 (0.4) | 12 (0.8) |

[a]2 cases were considered to be treatment-related

- The incidence rate of TEAEs by severity was similar between treatment groups **(Table 4)**
- Overall, most subjects reported TEAEs that were mild (68.0%, 232/341) or moderate (29.9%, 102/341) in severity
- 7 subjects (2.1%, 7/341) reported severe TEAEs
- All severe TEAEs were considered not related to the study medication by the investigator

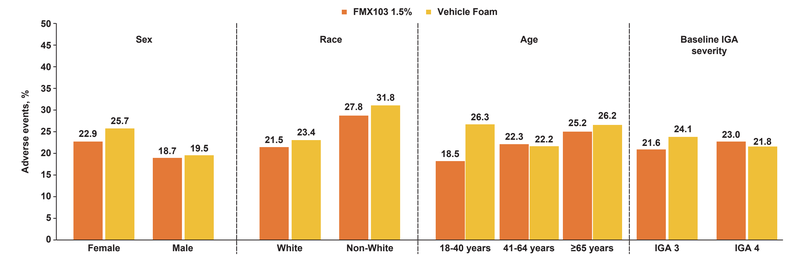
### Table 4. Summary of TEAEs by severity

| | FMX103 1.5% (n=1008) | | | | Vehicle Foam (n=513) | | | | Overall (N=1521) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OA | Mild | Mod | Sevr | OA | Mild | Mod | Sevr | OA | Mild | Mod | Sevr |
| Subjects reporting any TEAE, n (%)[a] | 219 (21.7) | 145 (14.4) | 71 (7.0) | 3[b] (0.3) | 122 (23.8) | 87 (17.0) | 31 (6.0) | 4[c] (0.8) | 341 (22.4) | 232 (15.3) | 102 (6.7) | 7 (0.5) |

Mod, moderate; OA, overall; Sevr, severe.
[a]Subjects experiencing one or more adverse events are counted only once for each adverse event term and counted only by the maximum severity. If severity is missing, it is counted as Severe.
[b]Rosacea, post-traumatic headache, application site pain.
[c]Fall, dyspnea, asthma, pyrexia, myocardial infarction.

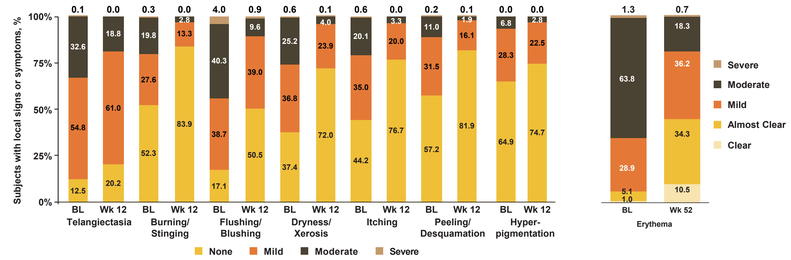
- Similar incidence rates of TEAEs were observed across both treatment groups for predefined subgroups **(Figure 6)**:
  - Sex
  - Race
  - Age
  - Baseline disease severity (IGA)

### Figure 6. Summary of overall percentages of AEs in all groups




- The majority of subjects in both treatment groups recorded local tolerability assessments as none or mild at both baseline and week 12 (Figure 7)
  - Similar rates of mild, moderate, and severe assessments were observed across both treatments and timepoints within each subgroup category
  - No notable differences were observed in facial tolerability assessments by subgroup
  - At week 12, all facial local tolerability assessments showed improvement compared to baseline
  - Notable improvements in erythema were observed, with the percentage of patients with clear or almost clear signs of erythema increasing from 6.1% at baseline to 44.8% at week 12

### Figure 7. Facial local tolerability assessments at baseline and week 12 in FMX103 1.5% treatment group




BL=baseline, N=1008; Wk 12=week 12, N=897; All symptoms were evaluated on a 4-point scale consisting of 0=none, 1=mild, 2=moderate, and 3=severe, except for erythema, which was evaluated on a 5-point scale consisting of 0=clear, 1=almost clear, 2=mild, 3=moderate, and 4=severe.

## Summary

### Efficacy Summary

- FMX103 1.5% demonstrated efficacy over vehicle foam in treating papulopustular rosacea in a pooled population of ~1500 subjects, with effects being observed as early as 4 weeks into treatment
- Sub-analyses were performed on the integrated data set to characterize the efficacy of FMX103 1.5% in treating papulopustular rosacea in predefined subgroups of subjects
  - FMX103 1.5% demonstrated significant efficacy benefits in treating papulopustular rosacea in subgroups of subjects that had either moderate (IGA=3) or severe (IGA=4) disease severity at baseline, with a more pronounced effect in the severe subpopulation
- Findings from this integrated efficacy analysis are thus consistent with those from the individual phase 3 studies, both of which achieved statistically significant differences for all primary efficacy endpoints and further demonstrated significant differences as early as 4 weeks into treatment

### Safety Summary

- FMX103 1.5% was generally safe and well tolerated
- 341 (22.4%) subjects reported a TEAE during the 2 identical double-blind Phase 3 studies
  - In general, no differences were observed between treatment groups in the incidence of TEAEs
  - The most frequently reported TEAEs for FMX103 1.5% vs vehicle, respectively, were viral upper respiratory tract infection (2.4% vs 2.3%), upper respiratory tract infection (1.9% vs 2.5%), and headache (1.4% vs 1.9%)
  - The majority of TEAEs reported were mild in severity (overall 68%)
  - 7 subjects reported severe TEAEs; all were considered to be unrelated to treatment, and were similar between treatment groups
- TEAEs were similar across clinically relevant subgroups, including sex, race, age, and baseline IGA score
- At week 12, all facial tolerability assessments had higher percentages of "none" compared to baseline and trended towards improving scores in the FMX103 1.5% treatment group

### Limitations

- A limitation of these studies relates to the generalizability of the data to a more ethnically diverse population, or to patients not conforming to the inclusion criteria of the studies
- An inclusionary criterion was to avoid common rosacea triggers, so efficacy would not be affected by such triggers

### Conclusions

- FMX103 1.5% demonstrated statistically significant differences compared with vehicle for both co-primary endpoints in a pooled population of two Phase 3 studies, and numerical advantages across clinically relevant subpopulations
- The results of the pooled safety analysis of 1,521 patients from two identical phase 3 studies demonstrated that FMX103 1.5% topical minocycline foam appeared to be safe and well tolerated with no serious treatment-related adverse events when administered daily for 12 weeks for the treatment of moderate-to-severe facial papulopustular rosacea

## Disclosures/Acknowledgment

**Disclosures**

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