Minocycline 1.5% foam for the topical treatment of moderate to severe papulopustular rosacea: Results of 2 phase 3, randomized, clinical trials

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Background: Efficacious topical medications for rosacea are needed. FMX103 1.5% is a novel topical minocycline foam that may have therapeutic benefits in treating rosacea while minimizing systemic adverse effects due to its topical route of delivery.

Objective: To determine the efficacy, safety, and tolerability of 12 weeks of treatment with FMX103 1.5% topical minocycline foam for papulopustular rosacea.

Methods: Two 12-week, phase 3, randomized, multicenter, double-blind, vehicle-controlled, 2-arm studies were performed in patients with moderate to severe papulopustular rosacea.

Results: Participants who received FMX103 1.5%, versus control individuals treated with vehicle, exhibited a significantly greater reduction in the number of inflammatory lesions (FX2016-11: -17.57 vs -15.65; P = .0031; FX2016-12: -18.54 vs -14.88; P < .0001) and higher rates of Investigator Global Assessment treatment success (FX2016-11: 52.1% vs 43.0%; P = .0273; FX2016-12: 49.1% vs 39.0%; P = .0077). No serious treatment-related treatment-emergent adverse events occurred.

Limitations: The generalizability of these data from a controlled clinical trial should be examined in a real-world setting.

Conclusions: FMX103 1.5% was efficacious for moderate to severe papulopustular rosacea and maintained a favorable safety profile. (J Am Acad Dermatol 2020;82:1166-73.)

Key words: double-blind clinical trial; facial; minocycline; papulopustular rosacea; phase 3; topical foam.

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IRB approval status: The study protocol (ClinicalTrials.gov identifier: NCT03142451) was approved by an institutional review board at each site.

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Rosacea is a chronic inflammatory cutaneous disorder involving the face that reportedly affects approximately 16 million individuals in the United States.[1,2] It is typically characterized by cutaneous signs such as flushing, central facial erythema, telangiectasia, edema, papules, and pustules.[1-3]

Currently approved topical therapies include azelaic acid, metronidazole, and ivermectin; each is a topical therapy approved by the US Food and Drug Administration for inflammatory lesions of rosacea.[2-5] They are generally well tolerated and, when effective, require continued use to maintain their therapeutic effects.[5] Oral tetracyclines, specifically doxycycline and minocycline, are also frequently used for the treatment of moderate to severe papulopustular disease but have been associated with systemic adverse effects involving the gastrointestinal tract and other body systems. Such effects from oral antibiotics may be circumvented by the use of topical therapy.[4,6]

FMX103 1.5% is a topical minocycline foam developed for the treatment of moderate to severe papulopustular rosacea. This formulation leverages the efficacy of minocycline while potentially reducing the risk of systemic adverse effects.[6] The foam is unique because it allows minocycline to exist as a suspended, micronized active ingredient, improving skin penetration[7] and avoiding a grainy sensation on the skin.[8] The main excipients (soybean oil, coconut oil, light mineral oil, and cyclomethicone 5) were chosen for their compatibility with minocycline and their association with moisturizing effects.[9-11]

Pharmacokinetic studies have evaluated the extent of systemic exposure with use of the minocycline foam formulation. A phase 1 pharmacokinetic study (FX2017-14) in which FMX103 1.5% was applied once daily topically for 14 days showed that this treatment yielded low plasma concentrations of minocycline over time (day 14 mean maximum concentration [C_{max}], 0.61 ng/ml), without systemic accumulation (FX2017-14). The relative bioavailability of minocycline plasma exposure of FMX103 1.5%, when compared to a single dose of 1 mg/kg oral minocycline (C_{max}, 850 ng/ml; FX2014-03), ranged from 0.072% to 0.124% based on the ratio of geometric mean C_{max} values (810-1384 times lower than oral minocycline).

A phase 2 study showed FMX103 1.5% to be efficacious, safe, and well tolerated for moderate to severe papulopustular rosacea over 12 weeks in more than 200 study participants.[6] FMX103 1.5% resulted in significant reductions in inflammatory lesions and improvement in scores on the Investigator's Global Assessment (IGA) from baseline.[6]

Reported here are the results of a phase 3 program consisting of 2 identical, double-blind studies conducted to further assess the efficacy, safety, and tolerability of FMX103 1.5% versus foam vehicle for the treatment of moderate to severe papulopustular rosacea.

CAPSULE SUMMARY

- Oral tetracyclines are recommended as first-line treatment for moderate to severe rosacea, but no topical tetracycline preparation is available.
- Two phase 3 clinical studies examined the efficacy and safety of FMX103 1.5%, a novel topical minocycline foam, in moderate to severe papulopustular rosacea.

METHODS

Study design

Two identical 12-week, randomized, multicenter, double-blind, vehicle-controlled, 2-arm studies were conducted (FX2016-11 and FX2016-12, hereafter referred to as *study 11* and *study 12*, respectively) at 100 study locations within the United States beginning in June 2017. Eligible individuals were randomly assigned 2:1 to receive FMX103 1.5% minocycline foam or vehicle foam. Participants applied treatment once daily for 12 weeks at approximately the same time each day. FMX103 1.5% or vehicle was applied as a thin layer over all areas of the face to ensure that the entire face was treated. Efficacy evaluations were performed at baseline and at weeks 4, 8, and 12; safety evaluations were performed at baseline and at weeks 2, 4, 8, and 12.

These studies were conducted in accordance with the principles of the Declaration of Helsinki and the principles of Good Clinical Practice and satisfied all applicable regulatory requirements per guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The study protocol (ClinicalTrials.gov identifier: NCT03142451) was approved by an institutional review board at each site, and all patients provided written informed consent after being given time to review the consent and have all of their questions addressed before enrollment.

Eligibility criteria

The studies enrolled men or women 18 years of age and older with moderate to severe papulopustular rosacea, defined as an IGA score of 3 (moderate) or 4 (severe), involving 15 to 75 facial papules and

Abbreviations used:

AE:	adverse effect
C_{max}:	maximum concentration
DRESS:	drug reaction with eosinophilia and systemic symptoms
IGA:	Investigator's Global Assessment
study 11:	FX2016-11
study 12:	FX2016-12
TEAE:	treatment-emergent adverse effect

pustules and no more than 2 facial nodules. Participants were required to have a history or presence of facial erythema and/or flushing and were directed to minimize exposure to external factors that might trigger rosacea flare-ups. Excluded were individuals with lesions involving the eyes and scalp, pregnant women, women who were lactating or planning a pregnancy, and individuals with excessive facial hair or with any skin condition that could interfere with the diagnosis or assessment of rosacea. Individuals with moderate or severe rhinophyma, dense telangiectasia, or plaque-like facial edema were not eligible. Also excluded were individuals who used the following: oral retinoids or vitamin A supplements within 6 months of randomization; topical retinoids to the face, systemic antibiotics, or systemic corticosteroids within 1 month of randomization; or topical antibiotics or corticosteroids within 2 weeks of randomization.

Efficacy and safety endpoints

The coprimary efficacy endpoints were the absolute change from baseline to week 12 in the inflammatory lesion count and the proportion of participants achieving endpoint success, defined as a dichotomized (yes/no) IGA score of 0 or 1 and at least a 2-grade improvement from baseline at week 12. The 5-point IGA scale (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe) was based on the severity of the rosacea, as indicated by the presence or absence of inflammatory papules, pustules, or nodules. Secondary endpoints included the dichotomized IGA score for endpoint success (where success was defined as a 2-grade improvement in score at week 12 compared with baseline), the absolute change from baseline in inflammatory lesion count at week 4 and week 8, and the percent change in the number of inflammatory lesions from baseline to week 12. Safety evaluations included adverse events (AEs), vital signs, physical examination, laboratory investigations, and local tolerability assessment.

Statistical analysis

It was estimated that a population size of 750 participants in each treatment arm would provide at least 90% power to detect a statistically significant difference in achievement of an IGA score of 0 or 1 and would be large enough to show statistically significant differences in effects on lesion counts. All efficacy endpoints were assessed for the intent-to-treat population. Missing data were imputed by using a multiple imputation methodology. The change from baseline in inflammatory lesion count was analyzed using an analysis of covariance model. The dichotomized IGA treatment success endpoint was analyzed using a Cochran-Mantel-Haenszel test. Secondary efficacy parameters were analyzed similarly to the coprimary efficacy endpoints. All hypothesis testing was conducted using 2-sided tests, with an $\alpha = .05$ level of significance. No statistical tests were performed for any of the safety assessments.

RESULTS

Baseline characteristics and participant demographics

A total of 751 participants (FMX103 1.5%, n = 495; vehicle foam, n = 256) were enrolled in study 11, and 771 participants (FMX103 1.5%, n = 514; vehicle foam, n = 257) were enrolled in study 12. Fig 1 shows the disposition of the participants. There were no notable differences in baseline demographics and disease characteristics between the FMX103 1.5% treatment group and the vehicle foam group in either study (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/kjcbyz6zfh.2#file-c7aef47b-16bf-4d01-878e-c91966073f6b). All participants had an IGA score for papulopustular rosacea indicating either moderate (study 11, 88.7%; study 12, 85.1%) or severe (study 11, 11.3%; study 12, 14.9%) disease.

Efficacy

Coprimary endpoint analysis. FMX103 1.5% met both coprimary endpoints at week 12 for both studies. FMX103 1.5% showed statistically significant reductions in the absolute inflammatory lesion count from baseline at week 12 compared with vehicle (study 11: -17.57 vs -15.65, $P = .0031$; study 12: -18.54 vs -14.88, $P < .0001$) (Fig 2, *A*) and was also superior to vehicle in meeting the IGA treatment success endpoint at week 12, with statistically significantly higher rates of endpoint success (study 11: 52.1% vs 43.0%, $P = .0273$; study 12: 49.1% vs 39.0%, $P = .0077$) (Fig 2, *B*).

Secondary endpoint analysis. In both studies, statistically significant reductions from baseline in

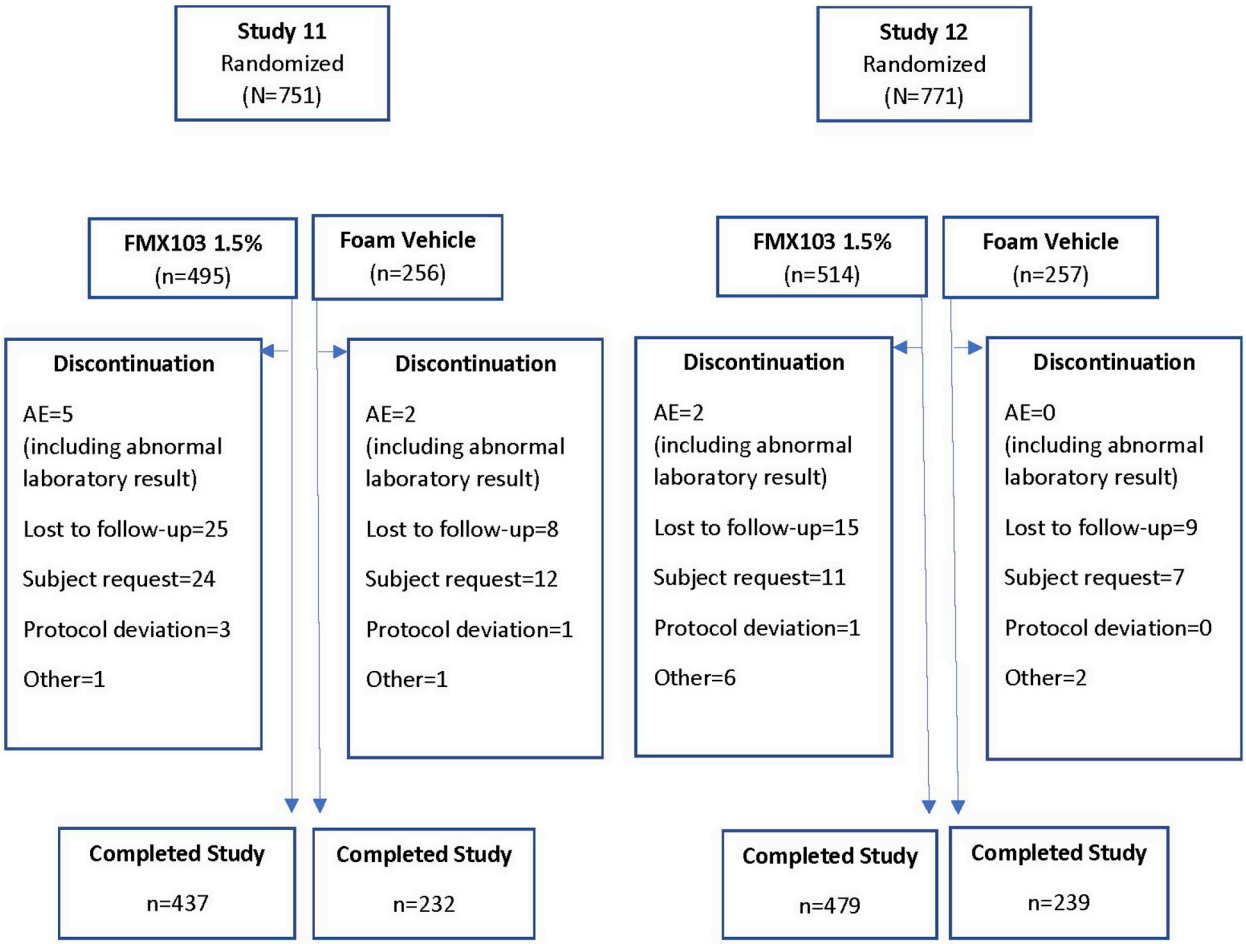


Fig 1. Summary of participant disposition. *AE*, Adverse event.

inflammatory lesions were observed as early as week 4 for FMX103 1.5% compared with vehicle for absolute change (study 11: -11.19 vs -8.79, $P = .0004$; study 12: -12.90 vs -8.74, $P < .0001$) and in the percent change (study 11: -39.9% vs -31.4%, $P = .0009$; study 12: -40.3% vs -28.5%, $P < .0001$) (Fig 2, *C*), which continued through to the end of treatment.

Furthermore, the proportion of participants achieving dichotomized IGA endpoint success from baseline to week 12 for FMX103 1.5% was significantly superior compared with that for vehicle foam for both study 11 (55.3% vs 45.8%, respectively; $P = .0171$) and study 12 (53.8% vs 45.1%, respectively; $P = .0189$).

Representative photographs of a study participant before and after treatment with FMX103 1.5% are shown (Fig 3). The majority of study participants were very satisfied or satisfied with FMX103 1.5% in terms of patient satisfaction (Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/9wbwnjfy2b.1#file-51212555-ffc6-483b-9ab4-68f1da63a63d), and the majority of participants treated with either FMX103 1.5% or vehicle foam rated their rosacea as slightly better or much better than before treatment during the participant global assessment at week 12.

Safety and tolerability

Daily application of FMX103 1.5% for 12 weeks appeared to be safe and well tolerated (Supplemental Table II; available via Mendeley at https://doi.org/10.17632/swmwxw4xyt.1#file-05e49f78-845a-4df4-9cde-241c97854ca3). There were no serious treatment-emergent AEs (TEAEs) in either study. The rate of participant discontinuation was low across both studies and was comparable for the FMX103 1.5% and vehicle groups. One participant in study 12 discontinued because of pruritus that was considered to be related to treatment (FMX103 1.5%). All other causes for discontinuation were not considered treatment related.

The most common noncutaneous TEAEs were viral upper respiratory tract infection (study 11: FMX103 1.5%, 1.8%; vehicle, 1.6%; study 12: FMX103 1.5%, 2.9%; vehicle, 3.1%), upper

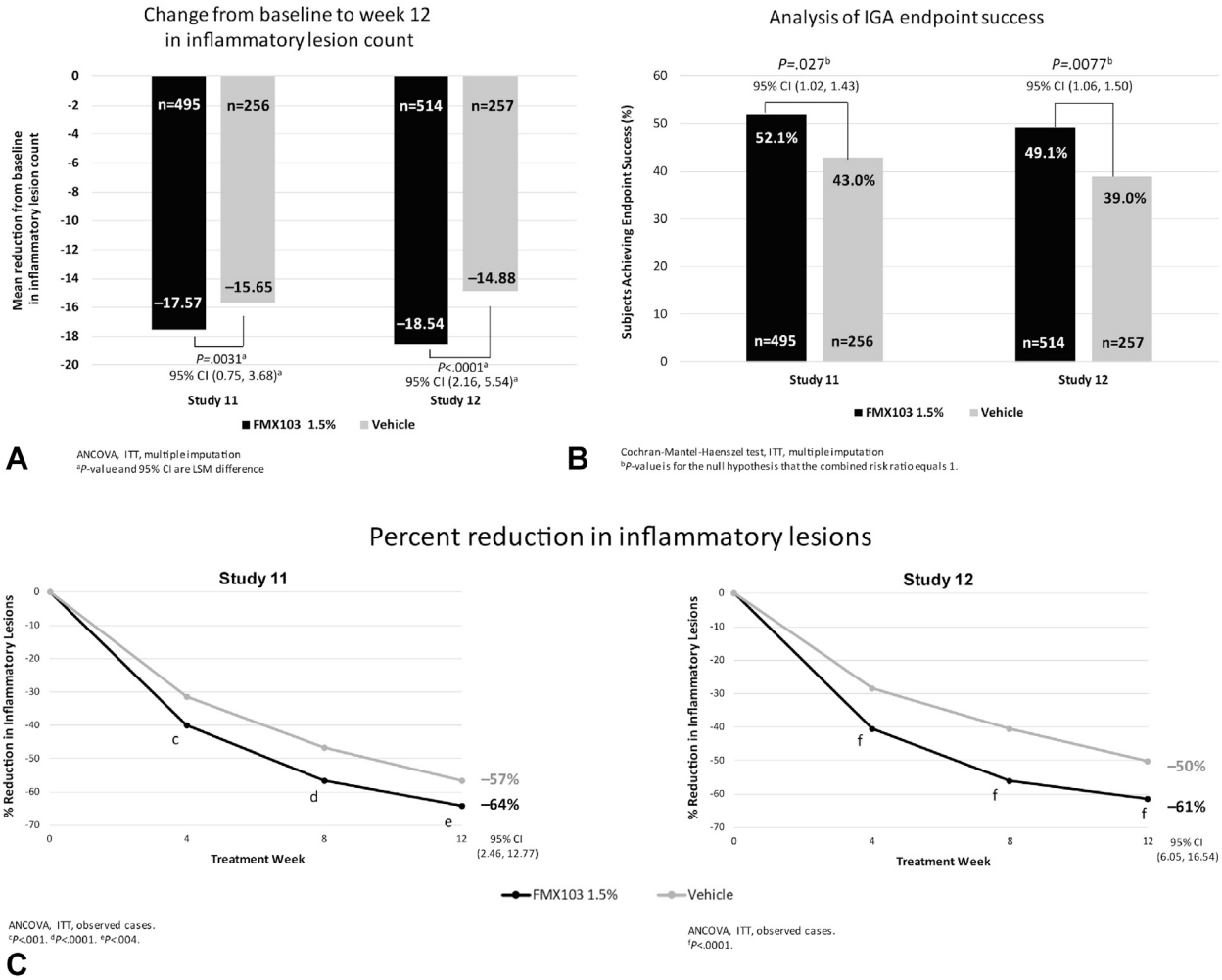


Fig 2. Efficacy endpoints at week 12. Mean reduction from baseline in (**A**) inflammatory lesion count, (**B**) proportion of participants with Investigator's Global Assessment endpoint success, and (**C**) percent change from baseline in inflammatory lesion count by visit. *ANCOVA*, Analysis of covariance; *CI*, confidence interval; *ITT*, intention to treat.

respiratory tract infection (study 11: FMX103 1.5%, 0.8%; vehicle, 2.0%; study 12: FMX103 1.5%, 2.9%; vehicle, 3.1%), and headache (study 11: FMX103 1.5%, 0.6%; vehicle, 1.6%; study 12: FMX103 1.5%, 2.1%; vehicle, 2.3%). The frequency of noncutaneous TEAEs was similar between both studies and in their respective treatment groups. The majority of the TEAEs were considered mild or moderate.

No cutaneous TEAEs were reported in 1% or more of participants in either study or treatment group. Of those that occurred, pruritus was the most common (study 11: FMX103 1.5%, 0.8% vs vehicle, 0.0%; study 12: FMX103 1.5%, 0.6% vs vehicle, 0.4%).

Among the 1008 participants who received at least 1 dose of FMX103 1.5%, more than 95% of participants reported no or only mild skin tolerability issues such as burning/stinging, flushing/blushing, dryness, itching, peeling, or hyperpigmentation (Tables I and II). More than 80% reported no or only mild telangiectasia or erythema at the application site after 12 weeks of treatment. For erythema specifically, across both studies and both treatment groups, the proportion of patients rated as clear (0) or almost clear (1) noticeably increased from baseline (4.3% to 6.6%) to week 12 (36.4% to 48.3%).

DISCUSSION

In both phase 3 studies (study 11 and study 12), FMX103 1.5% showed superiority to vehicle in the treatment of moderate to severe papulopustular rosacea. FMX103 1.5% met both coprimary endpoints, showing a statistically significant improvement vs vehicle at week 12 in absolute change from baseline in the inflammatory lesion

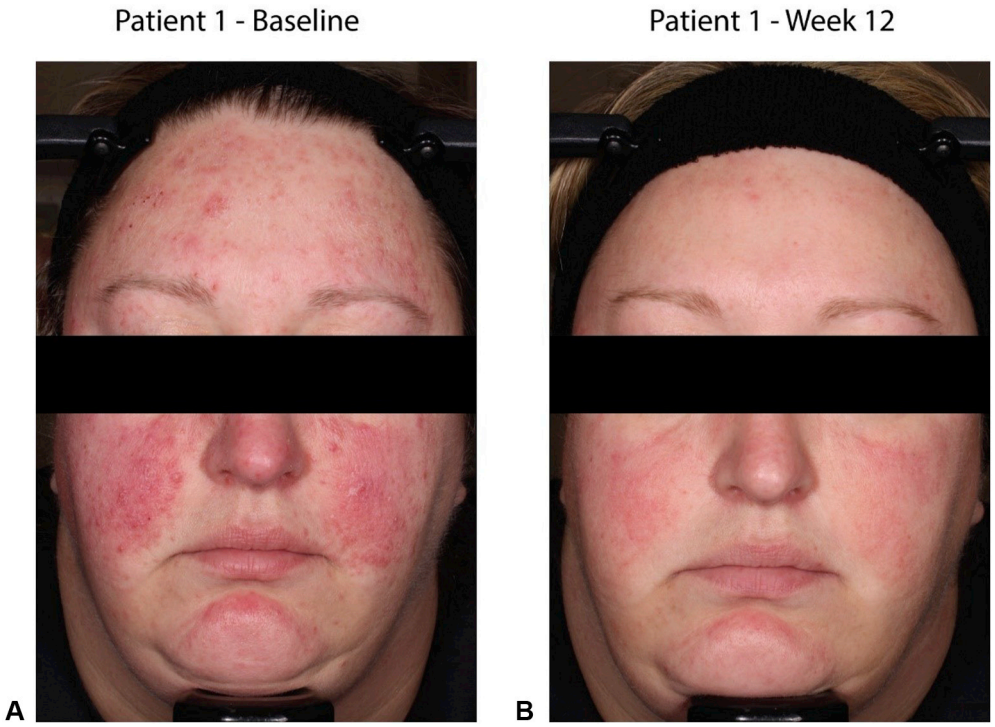


Fig 3. Representative clinical example. Photographs of a representative study participant (**A**) at baseline and (**B**) after weeks 12 of treatment with FMX103 1.5%.

count and rates of IGA endpoint success. The percent change from baseline in the number of inflammatory lesions was also significantly greater for FMX103 1.5% at week 12. Clinical efficacy was established as early as week 4 across both studies and was maintained throughout the duration of treatment in more than 1000 participants. Eligible participants from these 2 double-blind studies will be enrolled in study 13, an open-label extension study, to evaluate the safety and tolerability of topical minocycline 1.5% over an additional 40 weeks.

Oral therapies for rosacea are known to be associated with systemic adverse effects.[4,6] Common adverse effects with oral minocycline include vertigo; dizziness; and hyperpigmentation of the skin, mucous membranes, and teeth; it has also been linked to rare, yet serious, disorders such as drug reaction with eosinophilia and systemic symptoms (DRESS), drug-induced lupus-like syndrome, autoimmune hepatitis, and pseudotumor cerebri.[6,12] As a novel topical foam formulation of minocycline, FMX103 1.5% was specifically developed for the treatment of papulopustular rosacea. It has the potential to deliver the anti-inflammatory effects of minocycline,[13] which are of therapeutic benefit in rosacea, while reducing the risk of systemic adverse effects.[6]

The vehicle for FMX103 1.5% appeared to produce beneficial effects on both coprimary efficacy endpoints. The direct effects of vehicles on improving dermatologic diseases are common observations in topical therapy and, as such, cannot be viewed as true placebos. Vehicles that provide symptom relief, affect the efficient delivery of the active substance(s), and support patient compliance to therapy are increasingly important considerations in the development of any new topical formulation intended for direct application to the skin. As such, the role vehicles play in the overall treatment effect of any topical therapy is often as important as the active substance(s).

Although long-term use of oral minocycline has been associated with skin pigmentation in scars, inflammatory lesions, shins/forearms, and sun-exposed areas, in our study, there were no reported cases of pigmentation in nonapplication sites, and hyperpigmentation was similar from baseline to week 12 at the application site. Due to the local application of the formulation, we would not expect to see any of the pigmentary issues in the extremities and sun-exposed areas. Substantially longer periods of application might have resulted in pigmentation, but that is a limitation of this study and will be explored in the extension study.

Table I. Summary of facial local tolerability assessments at baseline and week 12 for study 11 (safety population)

	FMX103 1.5% (n = 494), n (%)				Vehicle (n = 256), n (%)			
Dermal tolerability	Nonmissing responses, n	Mild	Moderate	Severe	Nonmissing responses, n	Mild	Moderate	Severe
Erythema*								
Baseline	494	140 (28.3)	319 (64.6)	8 (1.6)	256	63 (24.6)	179 (69.9)	3 (1.2)
Week 12	423	169 (40.0)	80 (18.9)	1 (0.2)	225	86 (38.2)	55 (24.4)	2 (0.9)
Telangiectasia								
Baseline	494	289 (58.5)	145 (29.4)	0	256	157 (61.3)	74 (28.9)	0
Week 12	423	280 (66.2)	78 (18.4)	0	225	146 (64.9)	43 (19.1)	0
Burning/stinging								
Baseline	494	137 (27.7)	111 (22.5)	2 (0.4)	256	60 (23.4)	56 (21.9)	2 (0.8)
Week 12	423	71 (16.8)	16 (3.8)	0	225	39 (17.3)	3 (1.3)	0
Flushing/blushing								
Baseline	494	195 (39.5)	189 (38.3)	33 (6.7)	256	99 (38.7)	106 (41.4)	14 (5.5)
Week 12	423	186 (44.0)	36 (8.5)	7 (1.7)	225	94 (41.8)	20 (8.9)	2 (0.9)
Dryness/xerosis								
Baseline	494	178 (36.0)	120 (24.3)	5 (1.0)	256	91 (35.5)	71 (27.7)	0
Week 12	423	107 (25.3)	15 (3.5)	1 (0.2)	225	66 (29.3)	11 (4.9)	0
Itching								
Baseline	494	186 (37.7)	94 (19.0)	3 (0.6)	256	81 (31.6)	54 (21.1)	2 (0.8)
Week 12	423	89 (21.0)	15 (3.5)	0	225	50 (22.2)	10 (4.4)	0
Peeling/desquamation								
Baseline	494	150 (30.4)	43 (8.7)	2 (0.4)	256	80 (31.3)	29 (11.3)	0
Week 12	423	68 (16.1)	9 (2.1)	1 (0.2)	225	44 (19.6)	5 (2.2)	0
Hyperpigmentation†								
Baseline	494	134 (27.1)	29 (5.9)	0	256	73 (28.5)	12 (4.7)	0
Week 12	423	67 (15.8)	18 (4.3)	0	225	45 (20.0)	4 (1.8)	0

Percentages exclude missing responses.

*All local tolerability 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.

†Hyperpigmentation is most commonly used to describe localized postinflammatory darkening of the affected skin.

Nonetheless, this unique, lipophilic foam delivery of minocycline to the skin may allow attainment of the therapeutic benefits of minocycline without the risk of pigmentation. An additional 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. Participants were required to avoid common rosacea triggers to be included in the studies, but efficacy was not evaluated in relation to potential triggers.

FMX103 1.5% appeared to be safe and well tolerated across both studies (study 11 and study 12). Most TEAEs were mild to moderate, with the most common noncutaneous TEAE being viral upper respiratory tract infection and the most common cutaneous TEAE being pruritus. Serious TEAEs and participant discontinuations due to AEs occurred at a low rate; across both studies, only 1 patient discontinued because of a treatment-related TEAE (pruritus), which resolved after discontinuation. Skin tolerability issues at the application site were reported as none or mild for more than 80% of the participants.

CONCLUSIONS

The results of this study show that FMX103 1.5% topical minocycline foam appears to be an efficacious, safe, and well tolerated treatment for moderate to severe papulopustular rosacea. Data from 2 parallel, phase 3, randomized controlled trials met both coprimary endpoints (reduction in inflammatory lesions and improvement in the rate of IGA endpoint success) with statistically significant results compared with vehicle, providing evidence that this novel topical minocycline foam exhibits potential as an appropriate option for the topical treatment of moderate to severe papulopustular rosacea.

The authors would like to thank the patients and investigators who participated in the studies. Patients provided informed consent and waived their Health Insurance Portability and Accountability Act protection

Table II. Summary of facial local tolerability assessments at baseline and week 12 for study 12 (safety population)*

	FMX103 1.5% (n = 514), n (%)				Vehicle (n = 257), n (%)			
Dermal tolerability	Nonmissing responses, n	Mild	Moderate	Severe	Nonmissing responses, n	Mild	Moderate	Severe
Erythema†								
Baseline	514	151 (29.4)	324 (63.0)	5 (1.0)	257	72 (28.0)	163 (63.4)	5 (1.9)
Week 12	474	156 (32.9)	84 (17.7)	5 (1.1)	235	90 (38.3)	54 (23.0)	4 (1.7)
Telangiectasia								
Baseline	514	263 (51.2)	184 (35.8)	1 (0.2)	257	135 (52.5)	88 (34.2)	0
Week 12	474	267 (56.3)	91 (19.2)	0	235	126 (53.6)	48 (20.4)	0
Burning/stinging								
Baseline	514	141 (27.4)	89 (17.3)	1 (0.2)	257	76 (29.6)	53 (20.6)	0
Week 12	474	48 (10.1)	9 (1.9)	0	235	36 (15.3)	3 (1.3)	0
Flushing/blushing								
Baseline	514	195 (37.9)	217 (42.2)	7 (1.4)	257	101 (39.3)	103 (40.1)	9 (3.5)
Week 12	474	164 (34.6)	50 (10.5)	1 (0.2)	235	104 (44.3)	2 (10.6)	4 (1.7)
Dryness/xerosis								
Baseline	514	193 (37.5)	134 (26.1)	1 (0.2)	257	95 (37.0)	69 (26.8)	0
Week 12	474	107 (22.6)	21 (4.4)	0	235	55 (23.4)	13 (5.5)	0
Itching								
Baseline	514	167 (32.5)	109 (21.2)	3 (0.6)	257	92 (35.8)	50 (19.5)	0
Week 12	474	90 (19.0)	15 (3.2)	0	235	45 (19.1)	5 (2.1)	0
Peeling/desquamation								
Baseline	514	168 (32.7)	68 (13.2)	0	257	90 (35.0)	43 (16.7)	0
Week 12	474	76 (16.0)	8 (1.7)	0	235	44 (18.7)	5 (2.1)	0
Hyperpigmentation‡								
Baseline	514	151 (29.4)	40 (7.8)	0	257	84 (32.7)	14 (5.4)	0
Week 12	474	135 (28.5)	7 (1.5)	0	235	76 (32.3)	5 (2.1)	1 (0.4)

*Percentages exclude missing responses.
†All local tolerability 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.
‡Hyperpigmentation is most commonly used to describe localized postinflammatory darkening of the affected skin.

for the photographs included in this article (documentation on file). Writing assistance for this manuscript was provided by Scient Healthcare Communications.

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