A novel topical minocycline foam for the treatment of moderate-to-severe acne vulgaris: Results of 2 randomized, double-blind, phase 3 studies

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Background: FMX101 4% is a topical minocycline foam for the treatment of moderate-to-severe acne.

Objective: Evaluate the efficacy and safety of FMX101 4% in treating moderate-to-severe acne vulgaris.

Methods: Two identical phase 3 studies were conducted. Subjects were randomized 2:1 to once-daily FMX101 4% or foam vehicle for 12 weeks. The coprimary end points were the change in inflammatory lesion count from baseline and the rate of treatment success according to the Investigator's Global Assessment (a score of 0 or 1 for clear or almost clear, with a ≥2-grade improvement) at week 12.

Results: A total of 961 subjects were enrolled (study 04, N = 466; study 05, N = 495). Compared with vehicle, FMX101 4% demonstrated a significantly greater reduction in inflammatory lesions in both studies ($P < .05$) and a greater rate of treatment success in study 05 according to the Investigator's Global Assessment ($P < .05$). Pooled analyses of the 2 studies demonstrated statistical significance for both coprimary end points (all $P < .05$). Noninflammatory lesion count was also significantly reduced with FMX101 4% versus with vehicle in both studies. FMX101 4% was generally safe and well tolerated. Skin-related adverse events were reported in less than 1% of subjects treated with FMX101 4%.

Limitations: Longer-term efficacy and safety outcomes are needed (ongoing).

Conclusion: FMX101 4% topical minocycline foam significantly reduced both inflammatory and noninflammatory lesions and improved Investigator's Global Assessment scores in patients with moderate-to-severe acne. (J Am Acad Dermatol 2019;80:168-77.)

Key words: acne; clinical trial; dermatology; FMX101; minocycline foam; topical antibiotic.

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Funding sources: Sponsored by Foamix Pharmaceuticals.

Disclosure: Dr Stein Gold is an adviser and investigator for Foamix Pharmaceuticals, GlaxoSmithKline, LEO Pharma, and Valeant; an investigator for Janssen; and an adviser for Novartis. Dr Dhawan is an adviser for ABC Pharma. Dr Weiss is a principal investigator for AbbVie, Aclaris Therapeutics Inc, Endo International plc, Foamix Pharmaceuticals, Galderma Laboratories, LP, LEO Pharma US, Moberg Pharma North America LLC, Promius Pharma, LLC, and Valeant Pharmaceuticals International; a speaker for AbbVie and Ortho Dermatologics; a consultant for Aclaris Therapeutics Inc and LEO Pharma Inc; and an adviser for Foamix Pharmaceuticals, Galderma Laboratories, LP, and Valeant Pharmaceuticals International. Dr Draelos is a principal investigator and adviser for Foamix Pharmaceuticals. Dr Ellman and Dr Stuart are employees and stockholders of Foamix Pharmaceuticals.

Presented as a poster presentation at the 36th Fall Clinical Dermatology Conference, Las Vegas, NV, Oct 12-15, 2017.

Accepted for publication August 18, 2018.

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Published online August 27, 2018.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.08.020

Acne vulgaris (AV) is a chronic inflammatory skin disease characterized by inflammatory lesions (papules, pustules, and nodules) and noninflammatory lesions (blackheads and whiteheads). Almost everyone is affected by acne at some point in his or her life.[1] Acne can be associated with significant impairment of quality of life, even with mild severity, and it can lead to significant comorbidities, such as depression and anxiety.[1,2]

Minocycline and doxycycline of the tetracycline class of antibiotics are recommended by the American Academy of Dermatology guidelines as first-line therapies for moderate and severe acne.[1] Minocycline is a semisynthetic, second-generation tetracycline with antibacterial and anti-inflammatory properties and proven effectiveness in treating moderate-to-severe acne.[3,4] However, as with all oral antibiotics, there are concerns with systemic side effects, including autoimmune reactions and gastrointestinal reactions.[1,3] Topical clindamycin and erythromycin are available, but concerns about resistance have limited their general use.[5] In comparison, tetracyclines are less susceptible to resistance, with minocycline having the lowest resistance rate.[6-8] Currently, no topical minocycline is available.

The topical minocycline foam FMX101 4% was developed for its antibacterial and anti-inflammatory activity combined with minimization of the systemic side effects associated with oral administration. A pharmacokinetic study of once-daily FMX101 4% applied for up to 21 days demonstrated no significant systemic exposure or accumulation of minocycline.[9] In a phase 2 clinical trial in patients with moderate-to-severe acne, once-daily application of FMX101 4% for 12 weeks was associated with statistically significant and clinically meaningful improvements, along with a favorable safety and tolerability profile.[10]

A phase 3 program, consisting of 2 identical double-blind trials and a 40-week open-label phase, was initiated to further investigate the efficacy and safety of FMX101 4% in the treatment of moderate-to-severe AV. This report presents the results of the completed double-blind phase of this phase 3 program.

CAPSULE SUMMARY

- Topical tetracyclines, with their potent antibacterial and anti-inflammatory activity and potentially minimal systemic side effects, are an unmet need for acne therapy.
- Once-daily, FMX101 topical minocycline foam 4% appears to be safe, well-tolerated, and effective in treating moderate-to-severe acne; minocycline foam represents an important treatment option for patients with acne.

METHODS

Study design

Study 04 (NCT02815267) and study 05 (NCT02815280) were 2 identical phase 3, randomized, double-blind, multicenter (~30 sites), vehicle-controlled studies. Eligible subjects were randomized 2:1 to receive FMX101 4% or vehicle. The study treatment was self-applied once daily for 12 weeks, preferably in the evening. Efficacy and safety assessments were performed at weeks 3, 6, 9, and 12. At week 12, subjects could elect to continue into the open-label phase for an additional 40 weeks. Both studies were conducted in compliance with the principles of the Declaration of Helsinki and the principles of Good Clinical Practice and all applicable regulatory requirements, as per the International Council for Harmonisation of Technical Requirement for Pharmaceuticals in Human Use guidelines revised in 2016. The study protocol was approved by an institutional review board, and all patients provided written informed consent.

Eligibility criteria

Male or female individuals age 9 years or older were eligible if they had moderate-to-severe facial acne, as defined by an Investigator's Global Assessment (IGA) score of 3 or 4 and lesion counts of 20 to 50 inflammatory lesions (papules, pustules, and nodules), 25 to 100 noninflammatory lesions (open and closed comedones), and no more than 2 nodules. Female subjects who were pregnant, lactating, or planning to become pregnant during the study were excluded. Use of oral retinoids or corticosteroids within 12 weeks before randomization was prohibited, as was the use of topical retinoids, topical anti-inflammatory drugs and corticosteroids, oral antibiotics, or other systemic acne treatment within 4 weeks before randomization. Medicated facial cleansers or other topical medications for acne were not permitted to be used within 1 week of randomization. Subjects with any facial skin conditions that would interfere with clinical evaluations, including acne conglobate, acne fulminans, or secondary acne (chloracne or drug-induced acne) were excluded.

Efficacy and safety end points

The coprimary end points at week 12 were the absolute change in inflammatory lesion counts from baseline and the rates of IGA-assessed treatment success, which was defined as an IGA score of 0 or 1 (description of clear or almost clear) plus at least a

Abbreviations used:

AV: acne vulgaris
CI: confidence interval
IGA: Investigator's Global Assessment
LSM: least-square mean
RR: risk ratio
TEAE: treatment-emergent adverse event

2-grade improvement from baseline (Table I). Secondary end points included (1) the absolute change from baseline in noninflammatory lesion count at week 12 and (2) the absolute change from baseline in inflammatory lesion count and the proportion of subjects with treatment success according to IGA score at week 9 and at week 6. Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, physical examinations, clinical laboratory measurements, and application site tolerability. A subject satisfaction questionnaire was administered at the end of treatment.

Statistical analysis

With use of conservative estimates from phase 2 results, population sizes of 300 and 150 subjects for FMX101 4% and vehicle, respectively, were considered to provide greater than 90% power for a statistically significant difference. Efficacy parameters were assessed for all randomized subjects by using the last observation carried forward approach to impute missing values. The change from baseline in inflammatory lesion count was tested by analysis of covariance, and the dichotomized IGA score was tested by using the Cochran-Mantel-Haenszel test. Secondary end points (dichotomized IGA score for success and percent change in inflammatory lesion counts at week 12) were analyzed hierarchically. All hypothesis testing was conducted by using 2-sided tests with an α level of significance of 0.05. Safety parameters were assessed for all randomized subjects who took at least 1 dose of study drug. Safety assessments were summarized by treatment groups (no statistical tests were performed).

RESULTS

Baseline characteristics and subject disposition

A total of 961 subjects were enrolled in the studies (study 04, N = 466; study 05, N = 495). Figure 1 shows the disposition of the subjects. There were no significant differences between the treatment groups in baseline demographic or disease characteristics in either study (Table II). Across the 2 studies, the mean age ranged between 20.3 and 20.6 years and the majority of subjects were females. All subjects had an IGA score of moderate (study 04, 84.1%; study 05, 89.7%) or severe (study 04, 15.9%; study 05, 10.3%), with a broad range of total number of lesions allowed.

Table I. IGA scale for acne vulgaris

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions may be present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulocystic lesions)
3	Moderate	Many noninflammatory lesions. Multiple inflammatory lesions evident with several to many papules/pustules, and there may be 1 small nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent; many comedones and papules/pustules; there may be a few nodulocystic lesions
5	Very severe	Highly inflammatory lesions predominate; variable number of comedones; many papules/pustules and many nodulocystic lesions

Efficacy

FMX101 4% was significantly superior to vehicle in reducing inflammatory lesions (coprimary end point) from baseline in both study 04 (−14.13 vs −11.19 [least-squares mean (LSM) difference, 2.80; 95% confidence interval (CI), 0.72-4.88; P = .0083]) and study 05 (−13.46 vs −10.70 [LSM difference, 3.15; 95% CI, 0.95-5.35; P = .0051]) at week 12 (first coprimary end point) (Fig 2, *A*). FMX101 4% was significantly superior to vehicle for the second coprimary end point of IGA treatment success (subjects achieving IGA scores of clear or almost clear with a ≥2-grade improvement) in study 05 (14.66% vs 7.89% [risk ratio (RR), 1.88; 95% CI, 1.02-3.46; P = .0424]) but not in study 04 (8.09% vs 4.77% [RR, 1.72; 95% CI, 0.73-4.05; P = .2178]) (Fig 2, *B*). Reductions in inflammatory lesions were evident as early as week 3 with FMX101 4% in both studies, and the improvement was maintained through the end of treatment (Fig 3).

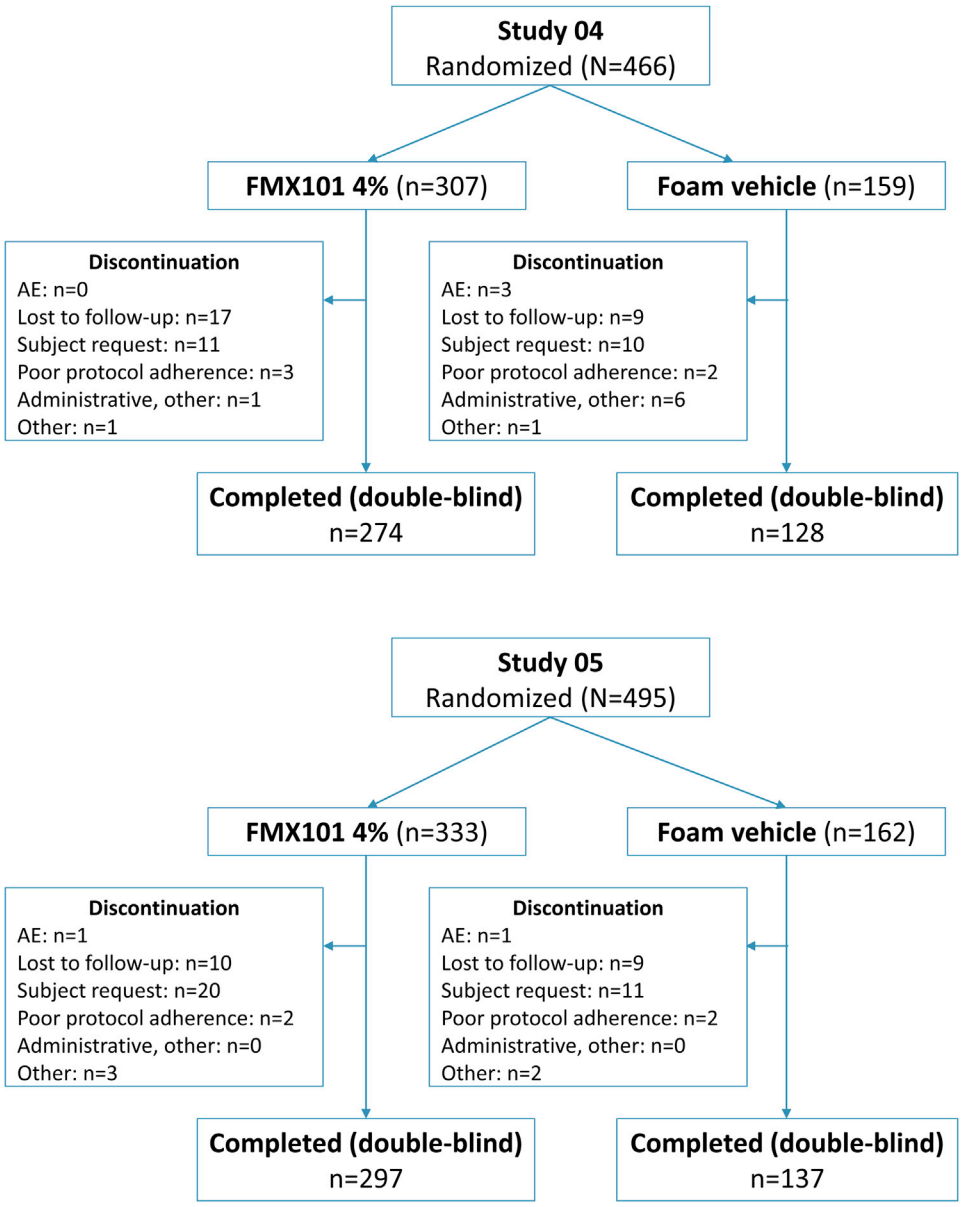

Fig 1. Subject disposition. *AE*, Adverse event.

FMX101 4% also resulted in significant reduction in noninflammatory lesions versus vehicle in both study 04 (−16.45 vs −10.30 [LSM difference, 5.49; 95% CI, 1.73-9.25; $P = .0042$]) and study 05 (−13.20 vs −7.00 [difference, 6.79; 95% CI, 0.58-13.00; $P = .0320$]) at week 12 (Fig 4).

Pooled data analyses

Data from the 2 identical studies were pooled, and post hoc analyses were performed for all 961 subjects. In the pooled analyses, FMX101 4% was significantly more effective than vehicle for both coprimary end points at week 12 (inflammatory lesion reduction from baseline, −13.79 vs −10.94 [LSM difference, 2.97; 95% CI, 1.44-4.49; $P = .0001$]; IGA treatment success, 11.51% vs 6.34% [RR, 1.81; 95% CI, 1.10-2.98; $P = .0188$]) (Figs 2 and 3). FMX101 4% also remained significantly better than vehicle in reducing noninflammatory lesions from baseline at week 12 (−14.76 vs −8.64 [LSM difference, 6.14; 95% CI, 2.47-9.82; $P = .0011$]) (Fig 4).

Safety and tolerability

Overall, FMX101 4% minocycline foam appeared to be safe and well tolerated across the 2 studies. A total of 113 TEAEs were reported in 17.4% of the subjects in study 04 (81 of 466), and 249 TEAEs were reported in 30.9% of the subjects in study 05 (153 of

Table II. Demographic and baseline characteristics

	Study 04		Study 05	
	FMX101 4% (n = 307)	Vehicle (n = 159)	FMX101 4% (n = 333)	Vehicle (n = 162)
Demographics				
Mean age, y (range)	20.3 (10-57)		20.6 (10-55)	
Male/female, n (%)	200 (42.9)/266 (57.1)		205 (41.4)/290 (58.6)	
Ethnicity, n (%)				
White	292 (62.7)		367 (74.1)	
Black or African American	126 (27.0)		103 (20.8)	
Asian	29 (6.2)		17 (3.4)	
Native Hawaiian or Other Pacific Islander	1 (0.2)		1 (0.2)	
Multiple races reported	18 (3.9)		7 (1.4)	
Disease characteristics				
Mean inflammatory lesion count, n (range)	32.2 (20-50)	31.6 (20-76)	31.5 (20-50)	32.3 (20-50)
Mean noninflammatory lesion count, n (range)	49.4 (25-100)	46.4 (25-98)	50.0 (25-102)	50.9 (26-104)
IGA score, n (%)				
3 (moderate)	255 (83.1)	137 (86.2)	296 (88.9)	148 (91.4)
4 (severe)	52 (16.9)	22 (13.8)	37 (11.1)	14 (8.6)

$P > .05$ for all comparisons.
IGA, Investigator's Global Assessment (0, clear; 1, almost clear; 2, mild; 3, moderate; and 4, severe).

495) (Table III); most of these events were mild or moderate.

The most common TEAEs occurring in at least 1% of subjects treated with FMX101 4% were headache (study 04, 2.3%; study 05, 6.0%), nasopharyngitis (study 04, 2.0%; study 05, 7.2%), upper respiratory infection (study 05, 1.8%), ligament sprain (study 05, 1.8%), blood creatinine phosphokinase level increased (study 04, 1.0%; study 05, 1.5%), pyrexia (study 04, 1.0%), nausea (study 05, 1.2%), and vomiting (study 05, 1.2%) (Table IV). Few skin-related TEAEs were reported (<1%) in the groups treated with FMX101 4% (Table IV), and most were mild. Treatment-related TEAEs were reported in 6 subjects (2%) and 9 subjects (2.7%) in the FMX101 4% treatment arm of study 04 and study 05, respectively (Tables III and V). Of these treatment-related TEAEs, 9 were skin-related TEAEs, of which 5 occurred in study 04 (ie, application site discoloration [n = 2], application site discomfort [n = 1], and yellowing of nails [n = 2]) and 4 occurred in study 05 (ie, application site discoloration [n = 3] and yellowing of the nails [n = 1]). In the FMX101 4% treatment groups, serious TEAEs were reported in 1 subject in study 04 and 4 subjects in study 05; none was considered treatment related (Tables III and V).

A total of 5 subjects discontinued on account of TEAEs; 1 subject was from the FMX101 4% treatment group (study 05, ectopic pregnancy), and 4 were from the vehicle group (study 04, application site acne, application site burn, application site erythema, and application site pruritus; study 05, increase in hepatic enzyme levels); none of these AEs were related to treatment. The majority of subjects (>84%) reported no or only mild dermal tolerability issues at the application site (Tables VI and VII). No increase in hyperpigmentation was noted. No clinically significant signals in clinical laboratory tests or vital signs were reported.

Subject satisfaction questionnaire

Overall, there was a high rate of subject satisfaction with use of FMX101 4%. A majority of subjects reported that they were satisfied or very satisfied with FMX101 4% as compared with the topical acne therapies that they had previously used (eg, gels, creams), as well as with the foam's ease of use and how it feels on the skin (Fig 5).

DISCUSSION

Extensive clinical evidence supported the use of the oral minocycline as a first-line therapy for patients with moderate-to-severe acne.[1,4] Nonetheless, there are still legitimate concerns with systemic adverse events associated with this route of administration.[1] A topical formulation of minocycline was expected to confer the advantages of facilitated local application and enhanced bioavailability while providing the drug's proven high efficacy in acne, all with less systemic toxicity than observed with its oral counterpart. Indeed, once-daily topical application of FMX101 4% minocycline foam for up to 21 days did not result in significant systemic exposure to minocycline or its accumulation.[9] In addition, phase 1 clinical studies in healthy subjects found no indication of phototoxicity

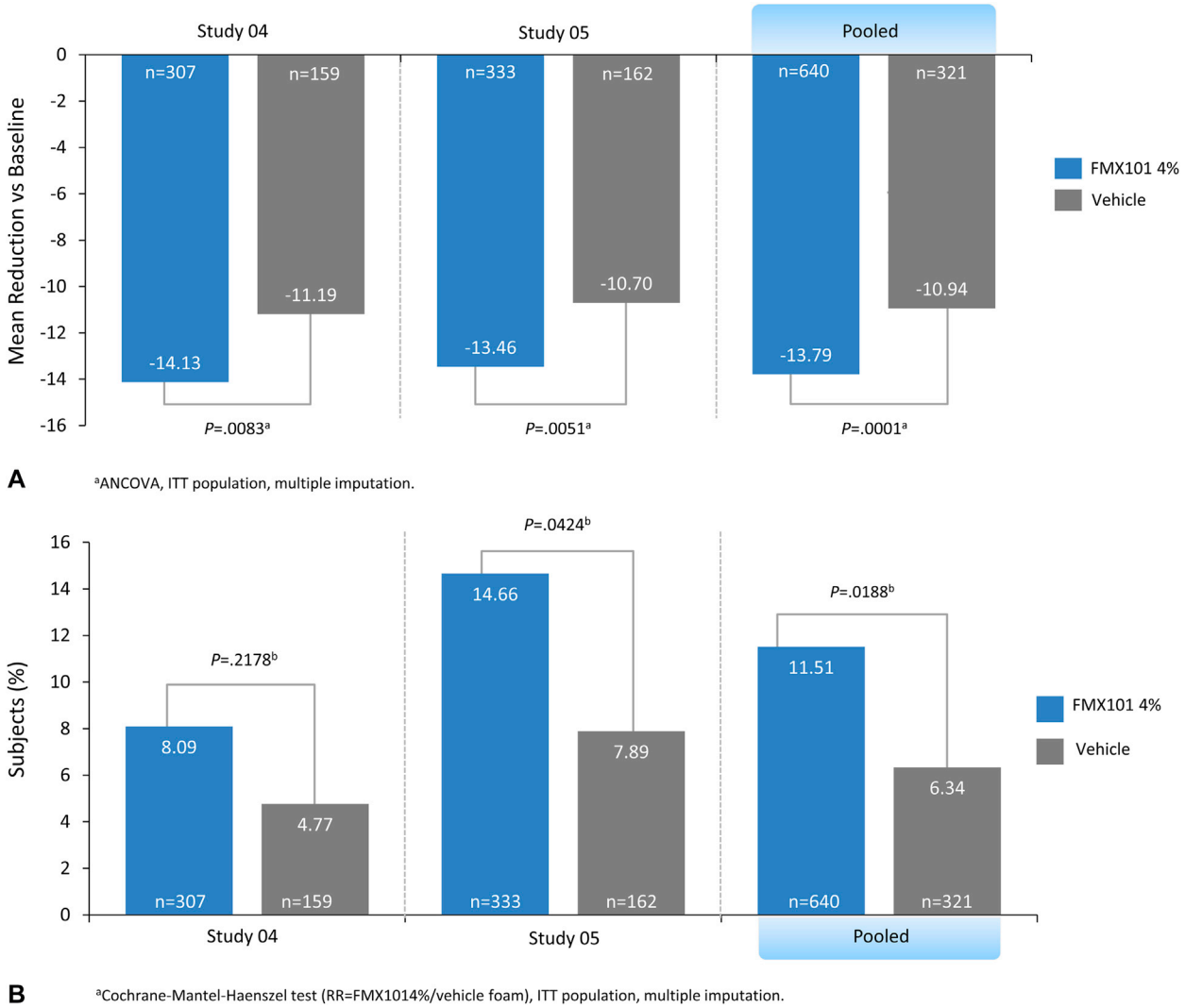

Fig 2. Coprimary end points. **A**, Absolute change in inflammatory lesion count from baseline at week 12 in study 04, study 05, and the pooled analysis. **B**, Proportion of subjects achieving treatment success according to the Investigator's Global Assessment (score of clear [0] or almost clear [1] with at least 2 grades of improvement from baseline) at week 12 in study 04, study 05, and the pooled analysis. [a]Analysis of covariance (ANCOVA) analysis, intent-to-treat (ITT) population, multiple imputation. [b]Cochrane-Mantel-Haenszel test (risk ratio [RR], FMX101 4%/vehicle), ITT population, multiple imputation.

or any evidence of skin irritation potential with topical minocycline foam (unpublished data).

In these studies, the once-daily application of FMX101 4% for 12 weeks was significantly more effective than vehicle in reducing inflammatory and noninflammatory lesions in both studies. Historical reports showed a 43% to 46% reduction of inflammatory lesions at 12 weeks from baseline with oral minocycline, in comparison with a reduction of 43% to 44% with FMX101 4% minocycline foam.[11] Notably, FMX101 4% appeared to provide a rapid onset of efficacy, with significant reductions of the inflammatory lesions observed as early as week 3 and maintained until the end of treatment. Compared with the vehicle, the rates of IGA-evaluated success of treatment with FMX101 4% were statistically significantly higher in study 05 and were numerically superior in study 04. This discrepancy may be attributed to an inadequate sample size, as the pooled analysis with all 961 subjects from both studies demonstrated statistical significance in favor of FMX101 4% for this end point. The overall rates of subjects with any TEAEs in study 04 and study 05 were 17.4% and 30.9%, respectively, as compared with 54% to 56% reported in clinical studies of oral minocycline.[11] Headache, which is a common TEAE

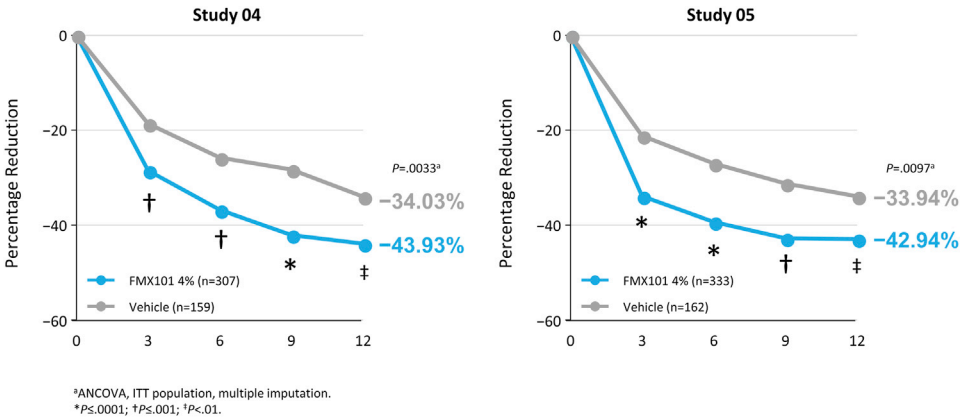

Fig 3. Percentage reduction in inflammatory lesion count from baseline by visit in study 04 and study 05. [a]Analysis of covariance (ANCOVA) analysis, intent-to-treat (ITT) population, multiple imputation. $^{*}P \leq .0001$. $^{\dagger}P \leq .001$. $^{\ddagger}P < .01$.

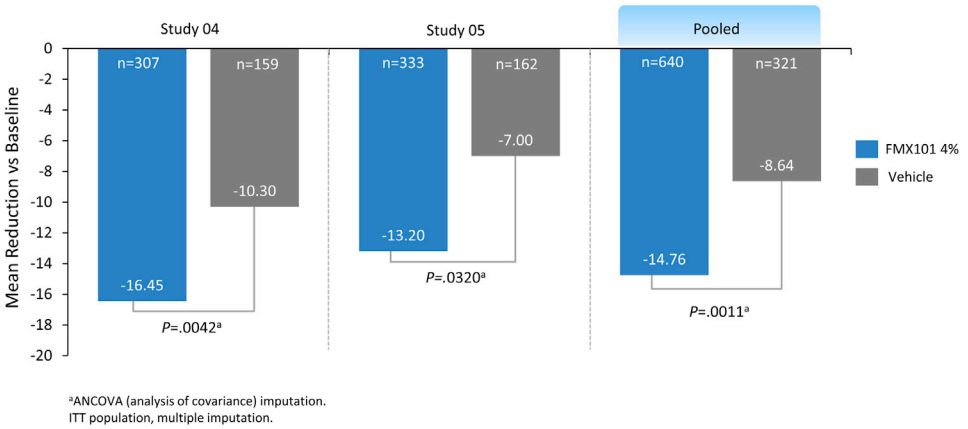

Fig 4. Absolute change in noninflammatory lesion count from baseline at week 12 in study 04, study 05, and pooled analysis. [a]Analysis of covariance (ANCOVA) analysis, intent-to-treat (ITT) population, multiple imputation.

and a side effect of oral minocycline (23%), was reported in only 2.3% and 6% of the subjects in the 2 studies with FMX101 4%.[11] Dizziness was reported in only 1 subject who received FMX101 4% in study 05. Only a few subjects using FMX101 4% (<1%) reported skin-related TEAEs, and most of these were mild. The rates of treatment-related TEAEs, serious TEAEs, and discontinuations were also very small across the 2 studies. Overall, FMX101 4% appeared to be an effective, safe, and well-tolerated treatment.

Poor patient adherence to acne treatment can be a pervasive problem.[12,13] Systemic acne therapy may have lower adherence rates than topical therapy, potentially because of dissatisfaction arising from the lack of efficacy and the occurrence of side effects.[13,14] The efficacy of the active drug and the potentially lower risk of systemic side effects with the topical minocycline foam may improve treatment adherence. In addition, the foam delivery system for topical drugs is easy to apply and does not leave a greasy or oily film on the skin after application. Previous surveys among patients have indicated that foams are generally preferred over creams, gels, and ointments.[15,16] Also, there were no solicited reports of fluorescence under black light with FMX101 4% (data not shown), a feature that was previously observed with other topical tetracyclines.[17] In the present studies, subjects were highly satisfied with using FMX101 4% foam formulation. Overall, the features of FMX101 4% that appealed to patients, together with the demonstrated efficacy and safety profile of minocycline, render the foam formulation an important addition to acne treatment options.

This study has several limitations. The 12-week duration may not have been adequate to demonstrate the long-term safety profile of topical minocycline. As

Table III. Adverse event profile

	Study 04		Study 05	
	FMX101 4% (n = 307)	Vehicle (n = 159)	FMX101 4% (n = 333)	Vehicle (n = 162)
Subjects with any TEAE, n (%)	52 (16.9)	29 (18.2)	110 (33.0)	43 (26.5)
Number of TEAEs	78	35	169	80
Subjects with any treatment-related TEAE, n (%)	6 (2.0)	4 (2.5)	9 (2.7)	3 (1.9)
No. of treatment-related TEAEs	7	6	10	4
Subjects with any TEAE leading to study discontinuation, n (%)	0	3 (1.9)	1 (0.3)	1 (0.6)
Number of TEAEs leading to discontinuation	0	4	1	1
Subjects with any serious AE, n (%)	1 (0.3)	0	4 (1.2)	2 (1.2)
Number of serious AEs	1	0	5	3

AE, Adverse event; *TEAE*, treatment-emergent adverse event.

Table IV. Profiles of skin-related and non–skin-related TEAEs

	Study 04		Study 05	
TEAE	FMX101 4% (n = 307)	Vehicle (n = 159)	FMX101 4% (n = 333)	Vehicle (n = 162)
Non–skin-related TEAEs in ≥1% of subjects, n (%)				
Headache	7 (2.3)	5 (3.1)	20 (6.0)	9 (5.6)
Nasopharyngitis	6 (2.0)	6 (3.8)	24 (7.2)	6 (3.7)
Creatinine phosphokinase level increased	3 (1.0)	1 (0.6)	5 (1.5)	4 (2.5)
Oropharyngeal pain	3 (1.0)	1 (0.6)	2 (0.6)	2 (1.2)
Pyrexia	3 (1.0)	0	0	0
Nausea	2 (0.7)	1 (0.6)	4 (1.2)	1 (0.6)
Upper respiratory tract infection	2 (0.7)	0	6 (1.8)	2 (1.2)
Cough	2 (0.7)	0	2 (0.6)	4 (2.5)
Ligament sprain	1 (0.3)	2 (1.3)	6 (1.8)	1 (0.6)
Vomiting	1 (0.3)	0	4 (1.2)	1 (0.6)
Vision blurred	0	0	2 (0.6)	3 (1.9)
Diarrhea	0	0	1 (0.3)	2 (1.2)
Alanine aminotransferase level increased	0	0	0	2 (1.2)
Dysmenorrhea	0	0	0	2 (1.2)
Administration site skin-related TEAEs, n (%)				
Application site discoloration	2 (0.7)	2 (1.3)	3 (0.9)	0
Dermatitis*	1 (0.3)	0	3 (0.9)	1 (0.6)
Local swelling	1 (0.3)	0	0	0
Application site discomfort	1 (0.3)	0	0	0
Application site burn	0	2 (1.3)	0	0
Rash†	0	1 (0.6)	2 (1.2)	2 (1.2)
Application site acne	0	1 (0.6)	1 (0.3)	0
Application site erythema	0	1 (0.6)	0	0
Application site pruritus	0	1 (0.6)	0	0
Dry skin	0	0	1 (0.3)	0
Eczema	0	0	1 (0.3)	0

TEAE, Treatment-emergent adverse event.
*Includes dermatitis, dermatitis contact, and application site dermatitis terms.
†Includes rash, generalized rash, and application site rash terms.

the adjunct to the current phase 3 program, the 9-month, open-label phase will evaluate the long-term durability of the efficacy and safety profiles observed in the 12-week double-blind phase. The lack of an active comparator arm is another limitation. According to historical reports, the rates of inflammatory lesion reduction with 12-weeks of oral minocycline or topical clindamycin and erythromycin have ranged between 10% and 60%.[11,18] Further head-to-head comparison studies will better differentiate the clinical significance of these medications in clinical practice. A limitation to

Table V. Treatment-related TEAEs and serious TEAEs profile

	Study 04		Study 05	
Subjects	**FMX101 4% (n = 307)**	**Vehicle (n = 159)**	**FMX101 4% (n = 333)**	**Vehicle (n = 162)**
Subjects with any treatment-related TEAE, n (%)	6 (2.0)	4 (2.5)	9 (2.7)	3 (1.9)
Application site discoloration	2 (0.7)	2 (1.3)	3 (0.9)	0
Yellowing of nails	2 (0.7)	0	1 (0.3)	1 (0.6)
Application site discomfort	1 (0.3)	0	0	0
Influenza-like illness	1 (0.3)	0	0	0
Headache	0	1 (0.6)	2 (0.6)	2 (1.2)
Application site acne	0	1 (0.6)	0	0
Application site erythema	0	1 (0.6)	0	0
Application site pruritus	0	1 (0.6)	0	0
Blood creatine phosphokinase level increased	0	0	1 (0.3)	0
Eye irritation	0	0	1 (0.3)	0
Lip dry	0	0	1 (0.3)	0
Nausea	0	0	1 (0.3)	0
Vision blurred	0	0	0	1 (0.6)
Subjects with any serious TEAE, n (%)	1 (0.3)	0	4 (1.2)	2 (1.2)
Suicide attempt	1 (0.3)	0	0	0
Intestinal obstruction	0	0	1 (0.3)	0
Intestinal perforation	0	0	1 (0.3)	0
Facial bone fracture	0	0	1 (0.3)	0
Ectopic pregnancy	0	0	1 (0.3)	0
Asthma	0	0	1 (0.3)	0
Biliary dyskinesia	0	0	0	1 (0.6)
Cholecystitis	0	0	0	1 (0.6)

TEAE, Treatment-emergent adverse event.

Table VI. Summary of tolerability assessments in study 04 at week 12 (safety population)

	FMX101 4% (n = 307)			Vehicle (n = 159)		
Dermal tolerability, n (%)	**0 None**	**1 Mild**	**2 Moderate**	**0 None**	**1 Mild**	**2 Moderate**
Erythema	248 (80.8)	19 (6.2)	0	124 (78.0)	4 (2.5)	0
Dryness	250 (81.4)	17 (5.5)	0	120 (75.5)	8 (5.0)	0
Hyperpigmentation	233 (75.9)	28 (9.1)	6 (2.0)	110 (69.2)	14 (8.8)	4 (2.5)
Skin peeling	259 (84.4)	8 (2.6)	0	125 (78.6)	3 (1.9)	0
Itching	254 (82.7)	12 (3.9)	1 (0.3)	124 (78.0)	3 (1.9)	1 (0.6)

Table VII. Summary of tolerability assessments in study 05 at week 12 (safety population)

	FMX101 4% (n = 333)			Vehicle (n = 162)		
Dermal tolerability, n (%)	**0 None**	**1 Mild**	**2 Moderate**	**0 None**	**1 Mild**	**2 Moderate**
Erythema	238 (71.5)	49 (14.7)	7 (2.1)	102 (63.0)	29 (17.9)	5 (3.1)
Dryness	281 (84.4)	11 (3.3)	2 (0.6)	124 (76.5)	11 (6.8)	1 (0.6)
Hyperpigmentation	237 (71.2)	44 (13.2)	13 (3.9)	118 (72.8)	15 (9.3)	3 (1.9)
Skin peeling	281 (84.4)	12 (3.6)	1 (0.3)	131 (80.9)	5 (3.1)	0
Itching*	274 (82.3)	18 (5.4)	2 (0.6)	123 (75.9)	12 (7.4)	0

*One subject in the vehicle group had severe itching.

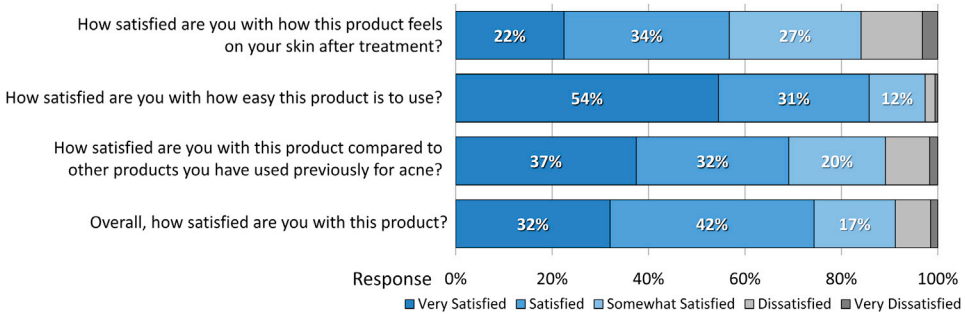

Fig 5. Results of the subject satisfaction questionnaire at week 12 (pooled analysis, N = 534).

interpreting the efficacy results in the present studies was the failure of FMX101 4% to meet the coprimary end point of IGA-assessed treatment success in study 04; although there was a clear numerical advantage (8.09% vs 4.77% for vehicle), there was no statistically significant difference. The pooled analysis of all 961 subjects did demonstrate the superiority of FMX101 4% over vehicle in this coprimary end point. The small number of subjects with severe acne who were enrolled in both studies (study 04, 15.9%; study 05, 10.3%) may preclude a clear interpretation of the effect of FMX101 4% in treating severe acne. To address these concerns, another phase 3 clinical study with approximately 1500 patients is currently under way.

CONCLUSIONS

In these phase 3 studies, once-daily topical application of FMX101 4% minocycline foam for 12 weeks resulted in reductions in both inflammatory and noninflammatory lesions and improvements in IGA score, with a favorable safety profile. Pooled analysis of both studies showed that FMX101 4% met all the coprimary end points. Analysis of the planned, long-term, open-label phase and further studies will determine the durability and the clinical significance of these outcomes.

The authors would like to thank the patients and investigators who participated in the study. Writing assistance for this manuscript was provided by Giang Nguyen, PhD, of *p*-value communications.

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