Topical Minocycline Foam (FMX-103) for the Treatment of Moderate-to-Severe Rosacea: Results of a Phase 2, Randomized, Double-Blind, Multicenter Clinical Study

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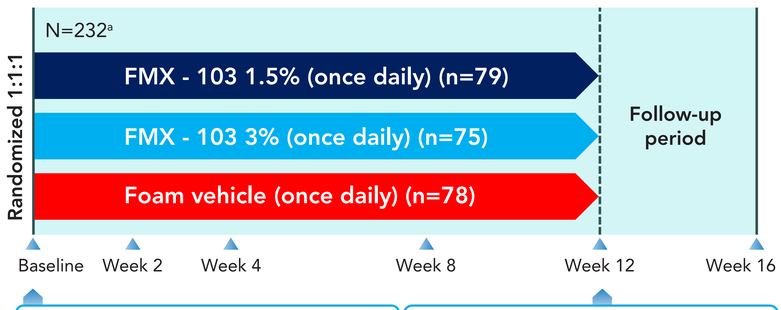
Introduction

- Rosacea is a chronic skin condition characterized by erythema, inflammatory papules/pustules, or telangiectasia. It is estimated to affect ~16 million people in the US[1,2]
- FDA-approved treatment for rosacea includes topical agents, such as metronidazole, azelaic acid, sulfacetamide 10%/sulfur 5%, and, recently, ivermectin, as well as oral doxycycline[1,3]
- Oral tetracyclines, particularly minocycline and doxycycline, may be prescribed for moderate-to-severe rosacea; however, their use is associated with systemic AEs[1,3]
- A novel, foam formulation of minocycline – FMX-103 – has been developed to facilitate local application and bioavailability of minocycline while preserving its efficacy for the treatment of rosacea
- This was a randomized, multicenter, double-blind study evaluating the safety and efficacy of 2 different doses of the topical minocycline foam, FMX-103 1.5% and 3%, in the treatment of papulopustular rosacea, as compared with vehicle

Methods

- Phase 2, randomized, multicenter (18 sites in Germany), double-blind, vehicle-controlled clinical trial
- Evaluated the safety and efficacy of 2 doses of a topical once-daily minocycline foam (FMX-103 1.5% and 3%) compared with vehicle foam in the treatment of moderate-to-severe papulopustular rosacea (Figure 1)
  - Subjects were randomized 1:1:1 to receive treatment once daily (in the evening) for 12 weeks
  - Safety and efficacy evaluations were performed at week 2, 4, 8, and 12, with an additional safety follow-up visit at week 16

Figure 1. Study design



Inclusion criteria
- Healthy males/nonpregnant females, aged ≥18 years
- Moderate-to-severe rosacea for ≥6 months, with ≥12 inflammatory facial lesions (papules/pustules)

Efficacy and safety end points
- **Absolute Δ inflammatory lesion count (primary end point)**
- IGA: ≥2-grade improvement; "clear" or "almost clear"
- Safety and tolerability

[a]A total of 233 subjects were randomized; however, 1 subject in the FMX-103 3% group did not receive treatment and was not included in the intent-to-treat analysis.

Results

- 232 subjects were randomized and received at least one dose of study drug (ITT population)
  - 201 (86.6%) subjects completed 12 weeks of treatment and the follow-up visit
- Baseline demographics and disease characteristics are shown in Table 1
  - ~50% to 60% of subjects had severe rosacea; the mean number of inflammatory lesions ranged from 30.6 to 34.5

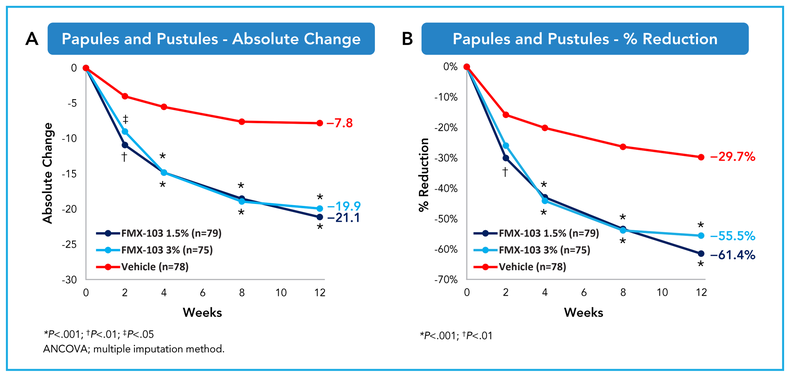
Table 1. Baseline demographics and disease characteristics

	FMX-103 1.5% (n=79)	FMX-103 3% (n=75)	Vehicle (n=78)	Overall (n=232)
Mean age, years (range)	51.2 (21-82)	51.6 (22-78)	54.8 (24-80)	52.5 (21-82)
Gender, %				
Male / Female	32.9 / 67.1	32.0 / 68.0	47.4 / 52.6	37.5 / 62.5
Race, %				
Caucasian	98.7	97.3	100.0	98.7
Other[a]	1.3	2.7	0	1.3
IGA of rosacea, %[b]				
Moderate (IGA=3)	43.0	38.7	51.3	44.4
Severe (IGA=4)	57.0	61.3	48.7	55.6
Mean (±SD) total inflammatory lesion count	34.5 (±20.89)	34.1 (±24.99)	30.6 (±15.48)	33.1 (±20.74)

[a]n=1 Other (FMX-103 1.5%); n=1 American Indian or Alaska Native, n=1 Native Hawaiian or Other Pacific Islander (FMX-103 3%).
[b]IGA grading for rosacea: 0=clear; 1=almost clear; 2=mild; 3=moderate; 4=severe.

- At week 12, both FMX-103 1.5% and 3% doses significantly reduced the number of papules and pustules vs vehicle (*P*<.001) (Figure 2A)
  - Significant reduction in lesion count was observed as early as week 2
- The corresponding percentage reductions in inflammatory lesions were 61.4% and 55.5% for FMX-103 1.5% and 3%, respectively, vs 29.7% for vehicle at week 12 (*P*<.001) (Figure 2B)

Figure 2. Change in inflammatory lesion counts from baseline by visit

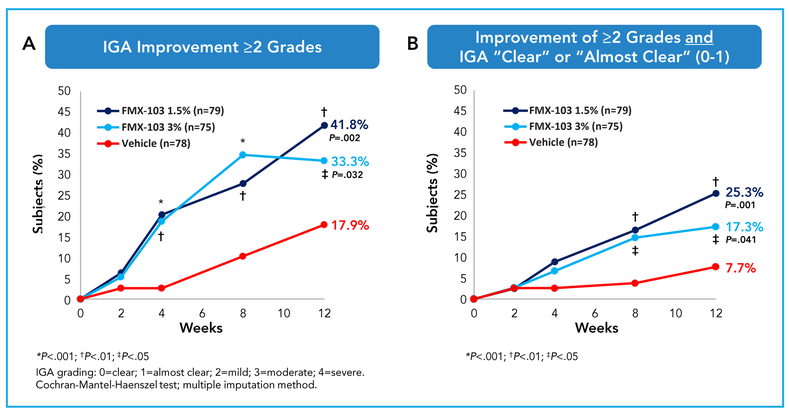


*P<.001; †P<.01; ‡P<.05
ANCOVA; multiple imputation method.

*P<.001; †P<.01

- Significantly more FMX-103 1.5% and 3% subjects achieved ≥2-grade improvement in IGA (Figure 3A) and IGA score of "clear" or "almost clear" vs vehicle at week 12 (Figure 3B)
  - Significantly more FMX-103 subjects had improvement of ≥2 IGA grades as early as week 4
- There was no statistically significant difference between the FMX-103 1.5% and 3% groups

Figure 3. Improvement in IGA score from baseline by visit



*P<.001; †P<.01; ‡P<.05
IGA grading: 0=clear; 1=almost clear; 2=mild; 3=moderate; 4=severe.
Cochran-Mantel-Haenszel test; multiple imputation method.

Safety

- Both FMX-103 1.5% and 3% doses appeared to be generally safe and well tolerated, with no reported treatment-related systemic AEs
  - Overall, 47% (109/232) of subjects reported ≥1 TEAE (Table 2)
  - The most common AEs (≥2% of subjects) included nasopharyngitis, urinary tract infection, cystitis, and bronchitis (Table 3)
  - 11 (4.7%) subjects reported treatment-related TEAEs; 9 had treatment-related dermal reactions (Tables 2, 4)
  - Serious TEAEs were reported in 4 subjects (3 in FMX-103 groups and 1 in vehicle group) (Tables 2, 4)
  - 4 subjects discontinued the study due to TEAEs; only 3 subjects discontinued due to dermal-related TEAEs (skin and subcutaneous tissue disorders) (Tables 2, 4)

Table 2. Summary of safety profile

Overall Summary of TEAEs, n (%)	FMX-103 1.5% (n=79)	FMX-103 3% (n=75)	Vehicle (n=78)
Subjects with ≥1 TEAE	46 (58.2)	32 (42.7)	31 (39.7)
Subjects with ≥1 treatment-related TEAE[a]	2 (2.5)	4 (5.3)	5 (6.4)
Treatment-related dermal reactions[b,c]	1 (1.3)	3 (4.0)	5 (6.4)
Subjects with ≥1 serious TEAE	2 (2.5)	1 (1.3)	1 (1.3)
Subjects with ≥1 TEAE leading to study discontinuation	0	3 (4.0)	1 (1.3)

Safety population includes all randomized subjects who applied at least one dose of study drug.
[a]Includes unassessable, possible, probable, and certainly related AEs.
[b]Includes skin and subcutaneous tissue disorders, and general disorders and administration-site conditions (ie, application-site erythema).
[c]Subjects experiencing ≥1 AE are counted only once for each AE term.

Table 3. Summary of TEAEs in ≥2% of subjects

Common TEAEs (≥2% of subjects), n (%)[a]	FMX-103 1.5% (n=79)	FMX-103 3% (n=75)	Vehicle (n=78)
Nasopharyngitis	11 (13.9)	3 (4.0)	9 (11.5)
Urinary tract infection	3 (3.8)	2 (2.7)	3 (3.8)
Cystitis	2 (2.5)	2 (2.7)	0
Bronchitis	3 (3.8)	0	0
Urinary tract infection bacterial	2 (2.5)	0	0
Influenza	0	0	2 (2.6)
Rosacea	2 (2.5)	3 (4.0)	0
Eczema	2 (2.5)	2 (2.7)	2 (2.6)
Hypertension	2 (2.5)	2 (2.7)	2 (2.6)
Eczema eyelids	2 (2.5)	0	0
Toothache	2 (2.5)	0	0
Headache	0	2 (2.7)	0

Safety population includes all randomized subjects who applied at least one dose of study drug.
[a]Subjects experiencing ≥1 AE are counted only once for each AE term.

Table 4. Summary of treatment-related dermal reactions, serious TEAEs, and TEAEs leading to study discontinuation

	FMX-103 1.5% (n=79)	FMX-103 3% (n=75)	Vehicle (n=78)
Subjects with treatment-related dermal reactions, n (%)[a,b]	1 (1.3)	3 (4.0)	5 (6.4)
Rosacea	0	2 (2.7)	0
Eczema	0	1 (1.3)	1 (1.3)
Skin exfoliation	0	1 (1.3)	0
Erythema	0	0	1 (1.3)
Pruritus	0	0	1 (1.3)
Scab	0	0	1 (1.3)
Skin burning sensation	0	0	1 (1.3)
Application-site erythema	1 (1.3)	0	1 (1.3)
Subjects with ≥1 serious TEAE, n (%)[b]	2 (2.5)	1 (1.3)	1 (1.3)
Hemorrhoids	0	1 (1.3)	0
Contusion	1 (1.3)	0	0
Cerebral hemorrhage	1 (1.3)	0	0
Hemiparesis	1 (1.3)	0	0
Pulmonary embolism	1 (1.3)	0	0
Gastroenteritis	0	0	1 (1.3)
Subjects with ≥1 TEAE leading to study discontinuation, n (%)[b,c]	0	3 (4.0)	1 (1.3)
Eczema	0	1 (1.3)	0
Rosacea	0	1 (1.3)	0
Pruritus	0	0	1 (1.3)
Skin burning sensation	0	0	1 (1.3)
Burning sensation	0	1 (1.3)	0

Safety population includes all randomized subjects who applied at least one dose of study drug.
[a]Includes skin and subcutaneous tissue disorders, and general disorders and administration-site conditions (application-site erythema).
[b]Subjects experiencing ≥1 AE are counted only once for each AE term.
[c]Eczema, rosacea, pruritus, and skin burning sensation were classed as skin and subcutaneous tissue disorders (dermal related); burning sensation was classified as a nervous system disorder.

Conclusions

- At week 12, both FMX-103 1.5% and FMX-103 3% were significantly better than vehicle in
  - Reducing the number of papules and pustules
  - Improving IGA score by ≥2 grades
  - Achieving IGA of "clear" or "almost clear" (score 0 or 1)
- Both FMX-103 doses appeared to be generally safe and well tolerated, with no reported treatment-related systemic AEs
  - Only 3 subjects discontinued the study due to dermal-related TEAEs
- These results indicated that FMX-103 appeared to be an effective, safe, and well tolerated treatment for moderate-to-severe papulopustular rosacea
- The results support further investigation in a larger, Phase 3 clinical trial

References

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Abbreviations:
AE=adverse event; TEAE=treatment emergent adverse event; IGA=Investigator's Global Assessment; ITT=intent-to-treat; SD=standard deviation.

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