Open-Label Extension Study Evaluating the Long-Term Safety, Efficacy, and Tolerability of FMX103 1.5% Topical Minocycline Foam in the Treatment of Moderate-to-Severe Facial Papulopustular Rosacea

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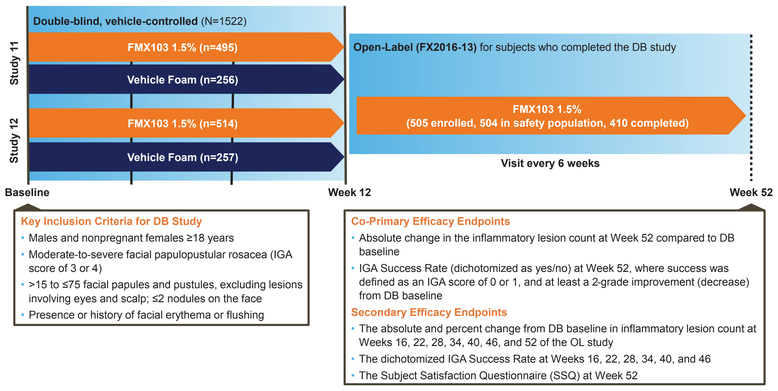
Introduction

- Rosacea is a chronic, inflammatory disorder involving the face that is characterized by central facial erythema, flushing, telangiectasia, edema, papules, and pustules[1-3]
- Oral tetracyclines, such as doxycycline and minocycline, are among the common therapies that are used for treating the disorder with oral, sub-microbial doxycycline currently approved for this indication. However, these agents have been associated with antibiotic resistance, adverse side effects, such as gastrointestinal upset and permanent hyperpigmentation, and following treatment cessation, the tendency for disease relapse is high[3-7]
- The efficacy and safety of FMX103 1.5% topical minocycline foam in treating moderate-to-severe rosacea have previously been reported in two, 12-week, double-blind, vehicle-controlled, Phase 3 studies (Study 11 and Study 12)[8]
- **Objective:** To demonstrate the long-term safety, tolerability and efficacy of topical FMX103 1.5% minocycline foam in moderate to severe facial papulopustular rosacea for up to 52 weeks.

Methods

- FX2016-13 (Study 13) was an open-label, multicenter, 40-week extension study to evaluate the long-term safety, tolerability, and efficacy of FMX103 1.5% topical foam in the treatment of moderate-to-severe facial papulopustular rosacea (**Figure 1**)
- Subjects were eligible to enter Study 13 upon successful completion of either double-blind study (Study 11 or Study 12)
  - There was no limit on the number of subjects who could enter the open-label phase
- Concomitant use of prescription or OTC medications that the subjects were taking or any change in dosage was permitted and recorded
- Investigator Global Assessments (IGAs) were based upon a 5-point scale with 0=clear, 1=almost clear, 2=mild, 3=moderate, and 4=severe

Figure 1. Study design



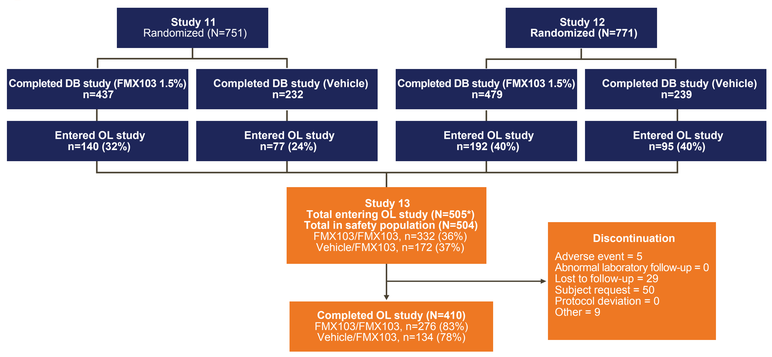
IGA, Investigator's Global Assessment; DB, double-blind study; OL, open-label study; OTC, over-the-counter.

Results

Subject Disposition and Double-Blind Baseline Demographics

- As shown in **Figure 2**, 504 subjects who completed the DB study (Study 11: N=217; Study 12: N=287) comprised the All Treated (Safety) population in the OL extension study (Study 13)

Figure 2. Subject disposition



*One subject who was enrolled discontinued the same day prior to taking the study drug and was therefore excluded from the safety population.

- Double-blind demographics, double-blind baseline characteristics, and concomitant use of medication during the OLE study are shown in **Table 1**

Table 1. Double-blind baseline demographics, disease characteristics, and concomitant use of medication

Variable	FMX103/ FMX103 (N=332)	Vehicle Foam/ FMX103 (N=172)	Overall (N=504)
Mean age (SD)	51.1 (12.62)	51.9 (11.90)	51.4 (12.37)
18 to 40 years	68 (20.5)	26 (15.1)	94 (18.7)
41 to 64 years	214 (64.5)	121 (70.3)	335 (66.5)
≥ 65 years	50 (15.1)	25 (14.5)	75 (14.9)
Gender, n (%)			
Male	91 (27.4)	62 (36.0)	153 (30.4)
Female	241 (72.6)	110 (64.0)	351 (69.6)
Race, n (%)			
White	321 (96.7)	163 (95.3)	484 (96.2)
Black	5 (1.5)	3 (1.8)	8 (1.6)
Other	6 (1.8)	6 (1.8)	12 (2.4)
Mean inflammatory lesion count, n (SD)	28.8 (12.63)	28.7 (11.93)	28.8 (12.38)
IGA score, n (%)			
3 – Moderate	301 (90.7)	149 (86.6)	450 (89.3)
4 – Severe	31 (9.3)	23 (13.4)	54 (10.7)
Any concomitant medication during the study, n (%)			
Vitamins	273 (82.2)	137 (79.7)	410 (81.3)
Lipid modifying agents	81 (24.4)	39 (22.7)	120 (23.8)
Agents acting on the renin-angiotensin system	76 (22.9)	38 (22.1)	114 (22.6)
Antibiotics and chemotherapeutics for dermatological use	72 (21.7)	35 (20.3)	107 (21.2)
Antifungals for dermatological use	6 (1.8)	4 (2.3)	10 (2.0)
Other dermatological preparations	6 (1.8)	1 (0.6)	7 (1.4)
	9 (2.7)	3 (1.7)	12 (2.4)

Baseline is defined as the Baseline visit in the double-blind study; IGA, Investigator's Global Assessment; SD, standard deviation.

Safety and Tolerability

- Summary of all adverse events in the all treated population is shown in **Table 2**
- The majority of the treatment-emergent adverse events (TEAEs) were considered mild or moderate in severity and no serious TEAEs were related to treatment

Table 2. Summary of TEAEs, rates of discontinuation and overall FMX103 1.5% treatment duration in the OL extension

Variable	FMX103 1.5%/ FMX103 1.5% (N=332)	Vehicle Foam/ FMX103 1.5% (N=172)	Overall (N=504)
Subjects with any AE, n (%)	151 (45.5)	70 (40.7)	221 (43.8)
Subjects with any TEAE, n (%)	137 (41.3)	64 (37.2)	201 (39.9)
Subjects with any serious TEAE, n (%)	9 (2.7)[a]	4 (2.3)[b]	13 (2.6)
Subjects with treatment-related TEAEs, n (%)	5 (1.5)[c]	8 (4.7)[d]	13 (2.6)
Subjects with serious treatment-related TEAEs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects discontinued due to AE, n (%)	3 (0.9)[e]	2 (1.2)[f]	5 (1.0)
TEAEs resulting in death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects exposed to ≥ 6 months (>168 days), n (%)	319 (96.1)	146 (84.9)	465 (92.3)
Subjects exposed to ≥ 1 year (>350 days), n (%)	272 (81.9)	0 (0.0)	272 (54.0)

Number (%) of subjects with at least 1 AE per category; AE, adverse event; TEAE, treatment-emergent adverse event
[a]Labyrinthitis, periorbital cellulitis, pneumonia, staphylococcal infection, cerebrospinal fluid leakage, cerebrovascular accident, syncope, subdural hematoma, death, hypokalemia, malignant melanoma
[b]Appendicitis perforated, post procedural hemorrhage, large intestinal instruction, chronic obstructive pulmonary disease
[c]Mydriasis, angular cheilitis, herpes simplex, dermatitis contact, hair color changes
[d]Diarrhea, conjunctivitis, sunburn, acne, dermatitis contact, erythema, pruritus, rosacea, skin lesion
[e]Dermatitis contact, mydriasis, enchondromatosis
[f]Rosacea, anemia, leukocytosis, appendicitis perforated, sepsis, appendicectomy

- TEAEs occurring in at least 2% of open-label subjects from either arm of the double-blind phase are shown in **Table 3**

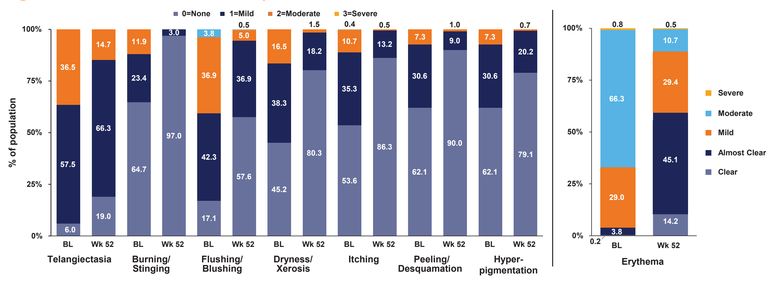
Table 3. TEAEs in the OL extension

Variable	FMX103 1.5%/ FMX103 1.5% (N=332)	Vehicle Foam/ FMX103 1.5% (N=172)	Overall (N=504)
Subjects with one or more TEAE, n (%)	137 (41.3)	64 (37.2)	201 (39.9)
Infections and infestations			
Upper respiratory tract infection	14 (4.2)	5 (2.9)	19 (3.8)
Viral upper respiratory tract infection	14 (4.2)	5 (2.9)	19 (3.8)
Sinusitis	8 (2.4)	9 (5.2)	17 (3.4)
Influenza	9 (2.7)	5 (2.9)	14 (2.8)
Bronchitis	8 (2.4)	2 (1.2)	10 (2.0)
Urinary tract infection	8 (2.4)	1 (0.6)	9 (1.8)
Nervous system disorders			
Headache	8 (2.4)	2 (1.2)	10 (2.0)
Vascular disorders			
Hypertension	7 (2.1)	1 (0.6)	8 (1.6)

TEAE, treatment-emergent adverse event

- Local facial assessments at Week 52 demonstrated that FMX103 1.5% topical minocycline foam was well tolerated during the OL extension study (**Figure 3**)

Figure 3. Facial tolerability assessed at Week 52

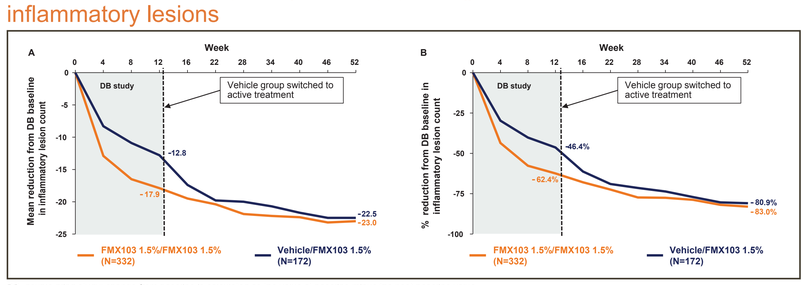


Note: Percentages exclude missing responses as 60 responses were missing from the FMX103/FMX103 group (N=272) and 43 responses were missing from the Vehicle/FMX103 group (N=129).
BL refers to baseline of the double-blind study
Hyperpigmentation was evaluated as post-inflammatory hyperpigmentation

Long-Term Efficacy

- Treatment with FMX103 1.5% during the 40-week OL extension study was associated with reduction in inflammatory lesions relative to the DB and OL baselines, regardless of previous treatment during the DB studies (**Figure 4**)

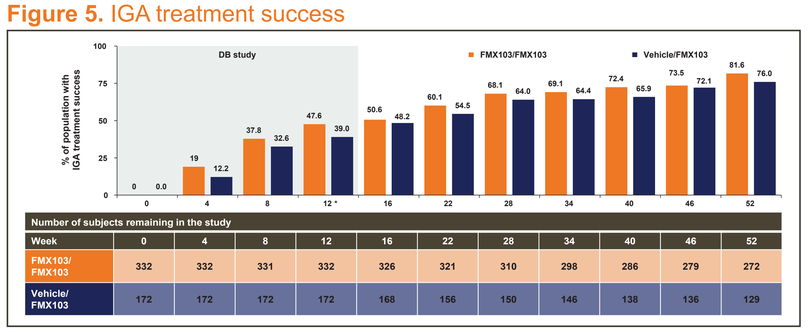
Figure 4. Absolute (A) and percent (B) change from DB baseline in inflammatory lesions



DB, double-blind study; change from baseline is calculated as the value at baseline minus the post-baseline value

- At the end of the study, 81.6% of the FMX103/FMX103 patients, and 76.0% of the vehicle/FMX103 patients, achieved IGA treatment success (**Figure 5**)

Figure 5. IGA treatment success



Number of subjects remaining in the study												
Week	0	4	8	12	16	22	28	34	40	46	52
FMX103/ FMX103	332	332	331	332	326	321	310	298	286	279	272
Vehicle/ FMX103	172	172	172	172	168	156	150	146	138	136	129

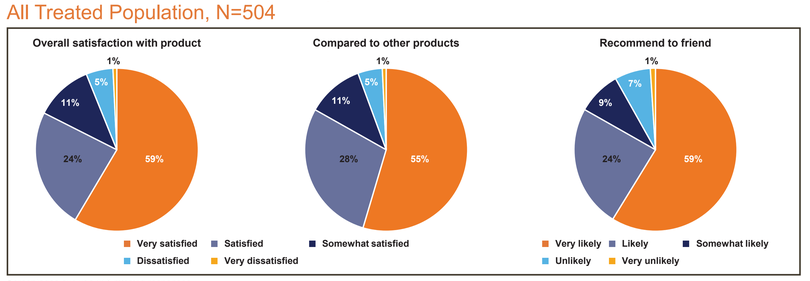
DB, double-blind study; IGA, Investigator's Global Assessment
*Week 12 of the DB study serves as the baseline for the OLE study

Subject Satisfaction

- At the end of the open-label study there was a high rate of subject satisfaction with FMX103 1.5% for the treatment of papulopustular rosacea (**Figure 6**)

Figure 6. Subject satisfaction questionnaire results at Week 52

All Treated Population, N=504



Percentages exclude 110 missing responses

Summary

Limitations

- Because of the nature of the open-label study, no inference can be made on comparability due to the absence of a vehicle-treated control

Conclusions

- FMX103 1.5% appeared to be safe and well tolerated for the long-term treatment of papulopustular rosacea for up to 52 weeks of treatment
- No minocycline-induced hyperpigmentation was observed
- Throughout 52 weeks of treatment, FMX103 1.5% continued to be associated with a decreasing number of inflammatory lesions, as well as with improvement in overall disease severity, as assessed by IGA scores
- Patient satisfaction levels were high, with >80% of all subjects being either satisfied or very satisfied with FMX103 1.5%

Disclosures/Acknowledgment

Disclosures
Dr. Stein Gold is an advisor and investigator for Foamix, Galderma, LEO Pharma, Novartis, and Valeant and is an investigator for Janssen, AbbVie, and Solgel and an advisor and investigator for Novartis. Dr. Del Rosso is a consultant for Aclaris, Almirall, Athenex, Cutanea, Dermira, Ferndale, Galderma, Genentech, LEO Pharma, Menlo, Novan, Ortho, Pfizer, Promius, Sanofi/Regeneron, SkinFix, and SunPharma; he has received research support from Aclaris, Almirall, Athenex, Botanix, Celgene, Cutanea, Dermira, Galderma, Genentech, LEO Pharma, Menlo, Novan, Ortho, Promius, Regeneron, SunPharma, and Thync; he receives honoraria from Aclaris, Celgene, Galderma, Genentech, LEO Pharma, Novartis, Ortho, Pfizer, Promius, Sanofi/Regeneron, and SunPharma; and he participates in speakers bureaus for honoraria from Aclaris, Celgene, Galderma, Genentech, LEO Pharma, Novartis, Ortho, Pfizer, Promius, Sanofi/Regeneron, and SunPharma. Dr. Bhatia is an investigator and consultant for Foamix Pharmaceuticals. Dr. Hooper served as an investigator for Foamix Pharmaceuticals; she reports personal fees from DelRicht Research during the conduct of the study; honoraria from Allergan, Almirall Aesthetics, Aqua Galderma USA, Cutera, Inc., Ferndale, La Roche Posay, Pixacore, RBC Consultants (clarisonic), Revance, and Vivisca!; and other financial benefits from Actavis, Dermira, GSK, Mylan, and Sol Gel. Dr. Nahm is an investigator for Foamix Pharmaceuticals. Dr. Iain Stuart is an employee and stockholder at VYNE Therapeutics Inc. This study is funded by Foamix Pharmaceuticals Ltd, a wholly owned subsidiary of VYNE Therapeutics Inc.

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