Design of a prospective, multicenter, randomized, evaluator-blinded study to evaluate the efficacy and safety of topical minocycline foam 4% with oral isotretinoin for the treatment of moderate-to-severe acne vulgaris

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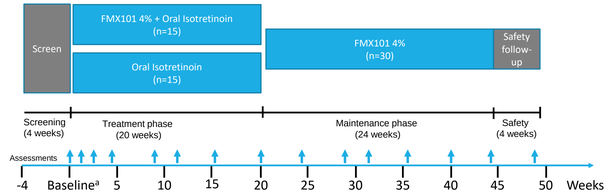
Background

- Acne vulgaris is a chronic skin disease affecting approximately 50 million people in the United States[1]
- Although systemic tetracyclines (eg, minocycline) are a mainstay in the treatment of moderate-to-severe acne, they are associated with potentially serious side effects[2-4]
- Topical antibiotics provide localized application to the pilosebaceous unit while minimizing systemic exposure[4]
- FMX101 is a topical lipophilic foam containing 4% minocycline that is FDA approved for the treatment of moderate-to-severe acne vulgaris[5]
- The efficacy, safety, and tolerability of FMX101 4% topical minocycline foam for the treatment of moderate-to-severe acne have been demonstrated in Phase 3 clinical studies[6]
- Oral isotretinoin is an established, FDA-approved treatment for severe acne; however, its teratogenicity requires careful monitoring and presents challenges for long-term use[7,8]
- The combination of oral isotretinoin and FMX101 4% may offer an improved treatment option for the long-term management of acne
- The objective of this study was to evaluate the efficacy, safety, and tolerability of concomitant use of FMX101 4% and oral isotretinoin compared with oral isotretinoin alone for the treatment of moderate-to-severe acne
- We also evaluated the efficacy of FMX101 4% as a maintenance therapy following discontinuation of oral isotretinoin

Methods

- A prospective, multicenter, randomized, evaluator-blinded study will be conducted in approximately 30 patients with inflammatory and noninflammatory acne lesions and moderate-to-severe acne per Investigator's Global Assessment (IGA) scores (IGA=3 or 4)
- Patients will be randomly assigned (1:1) to receive 20 weeks of concomitant FMX101 4% and once-daily oral isotretinoin treatment or oral isotretinoin treatment alone (**Figure 1**)
  - Oral isotretinoin will be initiated at a dose of 0.5 mg/kg/day for the first 4 weeks and increased to 1.0 mg/kg/day for the following 16 weeks
  - FMX101 4% will be applied once daily to the face and other acne-affected areas
- After this 20-week treatment phase, all patients will receive FMX101 4% for an additional 24-week maintenance phase
- Following the baseline visit, patients will return for weekly visits at Weeks 1 and 2 and then every 4 weeks from Weeks 4 to 44
- Patients who report any treatment-emergent adverse event (TEAE) will return for a safety evaluation 4 weeks after the maintenance phase

Figure 1. Study Design



Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Week	0	1	2	4	8	12	16	20	24	28	32	36	40	44	48

[a]Randomization occurred at the baseline visit (Visit 1, Week 0).

Eligibility Criteria

Key Inclusion Criteria

- Healthy males or nonpregnant females aged ≥12 years
- Facial acne vulgaris with an IGA score of moderate (3) or severe (4) (**Table 1**)
- Absence of systemic or dermatologic conditions that might increase the risk of adverse events or interfere with clinical evaluations
- If the female patient is of childbearing potential, 2 negative pregnancy tests, one being serologic, are required within the screening period
- Patients must be willing to minimize exposure of the treated skin to ultraviolet light (eg, avoid excessive sunlight, no use of tanning beds) and extremes in weather (eg, wind or cold) throughout the study

Key Exclusion Criteria

- History of isotretinoin use
- Allergy to tetracycline-class antibiotics or any ingredient in the study drug
- Use of the following medications within the specified time frame:
  - Medicated facial cleansers or topical acne treatments within 1 week of the baseline visit
  - Within 4 weeks of baseline, topical retinoids on the face, topical anti-inflammatories on the face, topical corticosteroids on extrafacial areas for ≥15 consecutive days and on ≥10% of body surface area, systemic antibiotics, and systemic acne treatments
  - Systemic corticosteroids or systemic retinoids within 12 weeks of baseline
- Use of hormonal contraceptives or testosterone replacement/supplementation for <3 months prior to the baseline visit

Table 1. IGA Scale of Acne Vulgaris

Score	Grade	Description
0	**Clear**	• No evidence of facial acne vulgaris
1	**Almost clear**	• Few open/closed comedones are present • A few papules/pustules may be present • No nodulocystic lesions are allowed
2	**Mild**	• Several to many open/closed comedones are present • A few papules/pustules are present • No nodulocystic lesions are allowed
3	**Moderate**	• Many open/closed comedones, papules/pustules are present • No nodulocystic lesions are allowed
4	**Severe**	• Significant degree of inflammatory disease • Papules/pustules are a predominant feature • A few nodulocystic lesions may be present • Open/closed comedones may be present

Study Endpoints

Co-primary Efficacy Endpoints

- Percent change from baseline in inflammatory lesion counts
- Percent change from baseline in noninflammatory lesion counts
- The proportion of patients with IGA treatment success (dichotomized as yes/no)
  - IGA treatment success is defined as an IGA score of 0 or 1 and at least a 2-grade improvement (ie, decrease) from baseline
- Efficacy evaluations will be performed at baseline and each subsequent visit
- Each patient's face will be photographed at each visit for efficacy assessments

Safety Endpoints

- Safety evaluations will be performed at every visit
  - Safety evaluations will include TEAEs, physical examinations, vital signs, and local skin tolerability assessments (**Table 2**)
  - TEAEs will be defined as events that emerge having been absent pretreatment, or worsen relative to the pretreatment state, and classified with respect to system organ class and preferred term using the Medical Dictionary for Regulatory Activities terminology
  - TEAEs will be volunteered, observed, and elicited by general questioning in a non-suggestive manner
- Safety analyses will be conducted on all randomized patients who used at least 1 dose of the study product (ie, safety population)
  - TEAEs, vital signs, physical examinations, local skin tolerability assessments, and clinical laboratory measurements will be summarized by treatment group using descriptive statistics
  - The number and percentage of patients reporting TEAEs will be summarized for each treatment group; a patient will be counted only once if he/she reports ≥1 events
  - For summaries of the relationship to the study drug and TEAE severity, a patient will be classified according to the closest relationship
  - For summaries of TEAE severity, a patient will be classified according to the highest severity

Table 2. Local Skin Tolerability Scale

Score	Grade	Dryness	Scaling	Erythema	Hyperpigmentation	Burning/Stinging	Itching
0	**None**	No dryness	No scaling	No signs of erythema	None	No burning/ stinging	None
1	**Mild**	Slight but definite roughness	Barely perceptible shedding, noticeable only on light scratching or rubbing	Slight pinkness present	Few scattered, small areas of light hyperpigmentation	Slight warm tingling/stinging sensation; not really bothersome	Sporadic itching lasting for a few moments to several minutes
2	**Moderate**	Moderate roughness	Obvious but not profuse shedding	Definite redness, easily recognized	Larger or more intense areas of hyperpigmentation	Definite warm, tingling/stinging sensation that is somewhat bothersome	Intermittent itching lasting for greater than 30 minutes
3	**Severe**	Marked roughness	Heavy scale production	Intense redness	Intense, extensive hyperpigmentation	Hot, tingling/stinging sensation that causes definite discomfort	Almost constant, intense itching lasting for several hours

Statistical Analysis

- Primary efficacy analyses will be conducted on the all-treated population (ie, all randomized patients)
  - Last observation carried forward methodology will be used to impute missing data
  - Changes from baseline in lesion counts will be calculated as the baseline value minus the post-baseline value; a positive change will reflect a reduction in lesion count
  - The percent change from baseline in inflammatory and non-inflammatory lesions at all visits will be analyzed using an analysis of covariance model with the main effect of treatment and baseline inflammatory lesion count and investigational site as covariates
  - IGA treatment success (ie, a 2-grade reduction leading to clear or almost clear) will be analyzed using a Cochran-Mantel-Haenszel test; there will be no stratification based on site
- The per-protocol (PP) population will be defined as the subset of the all-treated population without any protocol deviations that may have an impact on the efficacy assessments, as determined by the investigator prior to study unblinding
  - All analyses using the PP population will use the observed cases approach (ie, there will be no imputation for missing data at any time point)
- The 2 treatment groups will be tested at a 2-sided 0.05 level of significance without adjustment for multiplicity

Conclusions

- We hypothesize that maintenance therapy with FMX101 4% following oral isotretinoin will optimize long-term disease control with a favorable safety profile
- Limitations of this study will include the small sample size and the limited duration of the maintenance phase to evaluate durability of response
- Further studies are needed to examine sequence dosing of oral isotretinoin and FMX101 4% in the long-term management of acne

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Dr. Lain served as the principal investigator on these studies and has served as an advisor, investigator, and speaker for VYNE Therapeutics Inc. Dr. Lain is Chief Medical Officer, Sanova Dermatology, Executive Director & Principal Investigator, Austin Institute for Clinical Research. Dr. Carrasco, MD, is an investigator, consultant, and speaker for VYNE Therapeutics Inc.

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