Pharmacokinetic Evaluation of Once-Daily Topical 4% Minocycline Foam in Adult and Pediatric Subjects With Moderate-to-Severe Acne in Two Phase 1 Studies

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Background

- Acne vulgaris (AV) is a common skin disease that affects adolescents and can persist into adulthood[1]
- The mainstay of treatment for AV is systemic tetracyclines, such as doxycycline and minocycline[2]
- FMX101 4% is a novel topical foam formulation of minocycline. It has been shown to be an effective and well-tolerated treatment for moderate-to-severe AV in a Phase 2 clinical trial[3]
- Two Phase 1 studies were conducted to characterize minocycline pharmacokinetics (PK) and safety following multiple-dose administration of FMX101 4% minocycline foam in adult (**Study FX2014-03**) and pediatric (**Study FX2016-21**) patients with moderate-to-severe AV

Methods

- 2 Phase 1, single-center, nonrandomized, open-label studies (**Figure 1, Table 1**)
- Adults (age 18 to 35 years) or pediatric subjects (age 9 years to 16 years, 11 months) with moderate-to-severe AV
  - **Adult Study (FX2014-03)**: First received a single 1-mg/kg oral dose of oral extended-release minocycline HCl tablet (Solodyn®). Then, after 10 days, they received a once-daily topical application of 4 g FMX101 4% to the face, neck, upper chest, upper back, shoulders, and upper arms for 21 days
  - **Pediatric Study (FX2016-21)**: Received once-daily topical application of 4 g FMX101 4% to the face, neck, upper chest, upper back, shoulders, and upper arms for 7 days

Figure 1. Study Design

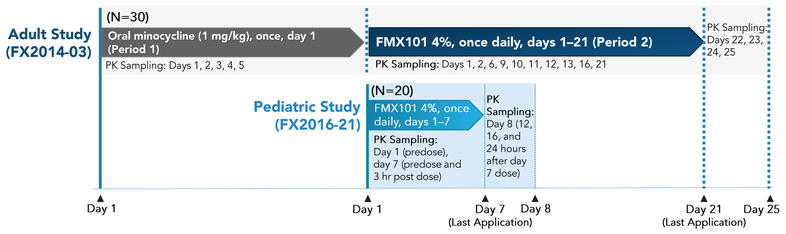


Table 1. Inclusion Criteria and Assessments

	Adult Study (FX2014-03)	Pediatric Study (FX2016-21)
Inclusion Criteria	• Healthy males/females aged 18–35 years • Moderate-to-severe facial AV (additionally affecting ≥2 regions of neck, upper chest, upper back, or arms) • BMI within 18.5-29.9 kg/m^2 ; body weight within 48.0-128.0 kg • Not pregnant, lactating, or planning a pregnancy during study	• Healthy males/females aged 9 years to 16 years, 11 months – Subjects <12 years: Mild facial acne and acne of limited extent – Subjects 12–16 years: Moderate-to-severe AV based on 5-point IGA scale and acne affecting ≥1 of the following: neck, upper chest, upper back, or arms • Sexually inactive, sterile, or using contraception
Blood Sampling for Drug Concentration	• Predose through 96 hours after administration of oral minocycline • Predose through 24 hours after FMX101 4% application on days 1, 12, and 21 • Prior to scheduled application on days 6, 9, 10, 11, and 16 • On and after Day 21, at 24 hours (Day 22), 48 hours (Day 23), 72 hours (Day 24), and 96 hours (Day 25) from last application of FMX101 4%	• On day 7, after 3, 12, 16, and 24 hours from last application of FMX101 4%
Pharmacokinetic Analyses	• PK parameters were calculated using noncompartmental methods • PK parameters included $AUC_{0\text{-inf}}$, $AUC_{0\text{-tau}}$, $AUC_{0\text{-tldc}}$, C_{max}, C_{24}, T_{max}, $T_{1/2}$, and accumulation ratio	• PK parameters were calculated using noncompartmental methods • PK parameters included $AUC_{0\text{-tau}}$, C_{max}, and C_{24}
Statistical Analyses	• Geometric mean was calculated for $AUC_{0\text{-inf}}$, $AUC_{0\text{-tau}}$, $AUC_{0\text{-tldc}}$, and C_{max}	• Geometric mean was calculated for $AUC_{0\text{-tau}}$ and C_{max}

$AUC_{0\text{-inf}}$=AUC from 0 to infinity.
$AUC_{0\text{-tau}}$=AUC during the 24-hour dosing interval.
$AUC_{0\text{-tldc}}$=AUC from 0 to time of last determinable concentration.
C_{24}=plasma minocycline concentration 24 hours after FMX101 4% application.
C_{max}=maximum plasma drug concentration.
$T_{1/2}$=terminal phase half-life.
T_{max}=time of maximum measured plasma drug concentration.
BMI=body mass index.
IGA=Investigator's Global Assessment.

References

1. Picardo M, et al. *Dermatol Ther* (Heidelb). 2017;7:43-52.
2. Zaenglein AL, et al. *J Am Acad Dermatol*. 2016;74:945-973.
3. Shemer A, et al. *J Am Acad Dermatol*. 2016;74:1251-1252.

Results

Baseline Demographics

- Baseline characteristics are shown in **Table 2**
- All adult subjects had moderate-to-severe AV
- A majority of pediatric subjects (90%) had moderate AV, and 1 subject had mild AV

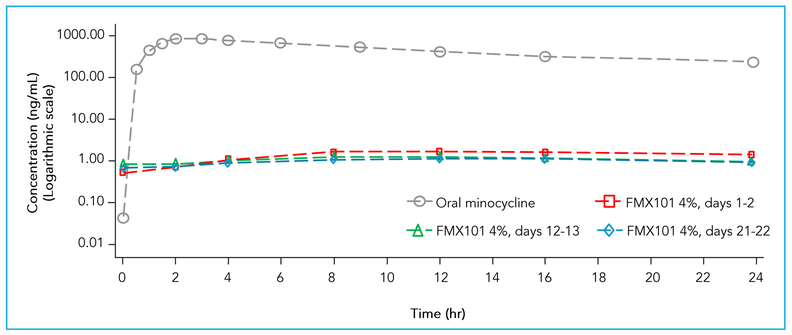
Table 2. Baseline Characteristics

	Adult Study (FX2014-03) (N=30)	Pediatric Study (FX2016-21) (N=20)
Mean age (range), yr	22.6 (18-30)	13.2 (10-16)
Gender, n (%)		
Male/Female	12 (40) / 18 (60)	9 (45) / 11 (55)
Race, n (%)		
White	27 (90)	7 (35)
Black or African American	3 (10)	13 (65)
Ethnicity, n (%)		
Hispanic/Latino	11 (36.7)	2 (10)
Non-Hispanic/Latino	19 (63.3)	18 (90)

Pharmacokinetics – Adults

- The mean plasma concentration of oral minocycline in adult subjects reached C_{max} by 3 hours after administration, followed by a log-linear decrease in concentration for the remaining 96-hour sample period
- The mean plasma minocycline concentration of FMX101 4% increased until 8–14 hours (median T_{max} value) on days 1, 12, and 21
- **Figure 2** shows a comparison of mean plasma minocycline concentrations during the first 24 hours after a single dose of oral minocycline and after topical applications of FMX101 4% at 3 timepoints in adult subjects
- In adult subjects, oral minocycline treatment had a geometric mean C_{max} of 850 ng/mL, while topical application of 4 g FMX101 4% in adults had a geometric mean C_{max} ranging from 1.109–1.539 ng/mL (days 1-2, days 12-13, and days 21-25)
- Steady state was achieved on day 6 of treatment

Figure 2. Mean Plasma Minocycline Concentration Over the First 24 Hours Following a Single Dose of Oral Minocycline and Topical Application of FMX101 4% (Semi-log Scale) in Adult Subjects (Study FX2014-03)



- In adults, minocycline exposure with daily topical application of FMX101 4% for 21 days was 730 to 765 times lower than that with oral minocycline (**Table 3**)

Table 3. Summary of Minocycline Relative Bioavailability With Oral Minocycline Administration (Reference) and Topical Application of FMX101 4% (Test) at Day 12 and Day 21 (Study FX2014-03)

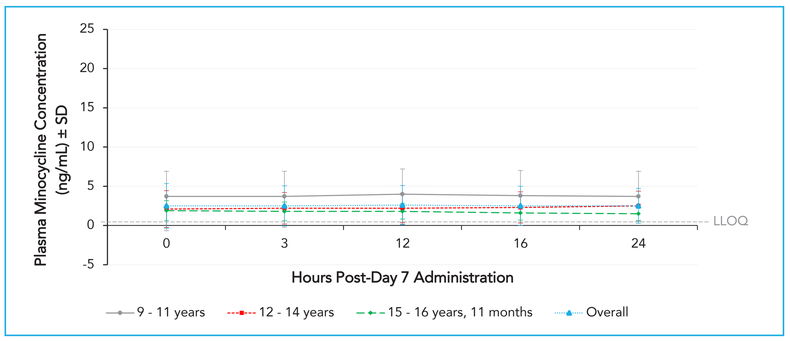
FMX101 4% vs Oral Minocycline	N	Geometric Mean[a] FMX101 4% (Test)	Geometric Mean[a] Oral Minocycline (Ref)	Geometric LSM Test/Reference Ratio,[b] % (90% CI)	1/GMR
Day 12 C_{max}	29	1.06	846	0.126 (0.100, 0.159)	794
Day 21 C_{max}	30	1.11	850	0.131 (0.113, 0.151)	763
Day 12 AUC[c]	29	20.06	14976	0.134 (0.110, 0.163)	746
Day 21 AUC[d]	30	20.07	15060	0.137 (0.121, 0.156)	730

[a]Geometric mean of oral minocycline and FMX101 4% based on LSM.
[b]Geometric LSM ratio and the associated 90% CI were back-transformed point estimates and the associated 90% CI.
[c]Day 12 $AUC_{0\text{-tau}}$ for FMX101 4% vs $AUC_{0\text{-inf}}$ for oral minocycline.
[d]Day 21 $AUC_{0\text{-tau}}$ for FMX101 4% vs $AUC_{0\text{-inf}}$ for oral minocycline.
CI=confidence interval; LSM=least squares mean; GMR=geometric mean ratio.

Pharmacokinetics – Pediatrics

- In pediatric subjects, the overall plasma concentrations of minocycline following the application of FMX101 4% once daily for 7 days were relatively constant over day 7 (~2.5 ng/mL) (**Figure 3**)

Figure 3. Mean Plasma Concentrations of Minocycline Following Application of FMX101 4% Once Daily for 7 Days in Pediatric Subjects (Study FX2016-21)



LLOQ=lower limit of quantification; SD=standard deviation.

- There were no substantial differences in mean concentrations of minocycline among the 3 pediatric cohorts (**Table 4**)
  - Across all cohorts, the geometric mean C_{max} value was 2.4 ng/mL

Table 4. Pharmacokinetic Parameters of Minocycline in Plasma in Pediatric Acne Subjects Treated With FMX101 4% (Study FX2016-21)

Age Group	N	Geometric Mean C_{max} (ng/mL)	Geometric Mean $AUC_{0\text{-tau}}$ (ng*hr/mL)	Geometric Mean C_{24} (ng/mL)	T_{max} (hr)[a]
9–11 years	6	3.522	68.175	2.933	12 (0,24)
12–14 years	8	2.250	42.167	1.998	20 (0,24)
15–16 years, 11 months	6	1.735	35.067	1.302	6 (0,24)
Overall	20	2.381	46.087	1.972	12.1 (0,24)

[a]Median (minimum, maximum) shown for T_{max}.

Safety

- In both adult and pediatric subjects, daily application of FMX101 4% was found to be safe and well tolerated (**Table 5**)
  - No adult or pediatric subjects experienced a serious treatment-emergent adverse event (TEAE), treatment-related TEAEs, or a TEAE leading to withdrawal from the study
  - 9 adult subjects in the FMX101 4% group reported 1 or more TEAES; all were mild or moderate in intensity (**FX2014-03**)
  - A single pediatric subject experienced 2 unrelated TEAEs (nausea and vomiting) (**FX2016-21**)

Table 5. Overall Summary of TEAEs Following Administration of Oral Minocycline and Topical Application of FMX101 4% in Adult and Pediatric Subjects

	Adult Study (FX2014-03) Oral Minocycline (N=30)	Adult Study (FX2014-03) FMX101 4% (N=30)	Pediatric Study (FX2016-21) FMX101 4% (N=20)
Subjects with any TEAE, n (%)	**2 (6.7)**	**9 (30.0)**	**1 (5.0)**
Dysmenorrhea	0	2 (6.7)	-
Nasal congestion	0	2 (6.7)	-
Rhinorrhea	0	2 (6.7)	-
Asthma	0	1 (3.3)	-
Bronchitis	0	1 (3.3)	-
Cough	1 (3.3)	0	-
Dermatitis contact	0	1 (3.3)	-
Headache	1 (3.3)	0	-
Oropharyngeal pain	0	1 (3.3)	-
Pharyngitis streptococcal	0	1 (3.3)	-
Respiratory tract congestion	0	1 (3.3)	-
Tonsillitis	0	1 (3.3)	-
Nausea	-	-	1 (5.0)
Vomiting	-	-	1 (5.0)

Conclusions

- In adult subjects, mean minocycline AUC and C_{max} values were substantially lower following the daily topical application of 4 g FMX101 4% for 21 days in comparison with a single dose of oral minocycline (~1 mg/kg)
- There was no evidence of accumulation in adult subjects receiving daily topical application of FMX101 4% for up to 21 days
- In pediatric subjects, mean minocycline C_{max} and AUC values following the daily topical application of 4 g FMX101 4% for 7 days were 2.4 ng/mL and 46.1 ng*hr/mL, respectively; these values were comparable to those seen in adults, 1.5 ng/mL and 20.1 ng*hr/mL, respectively, indicating similar minimal systemic exposure
- Pediatric subjects in all 3 age cohorts had similar levels of minocycline (~2.5 ng/mL) across the dosing interval with daily application of FMX101 4% for 7 days
- Once-daily topical application of FMX101 4% for 7 days and 21 days was shown to be safe and well tolerated in pediatric and adult subjects, respectively

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