

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 adulthood¹
- The mainstay of treatment for AV is systemic tetracyclines, such as doxycycline and minocycline²
- 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 trial³
- 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

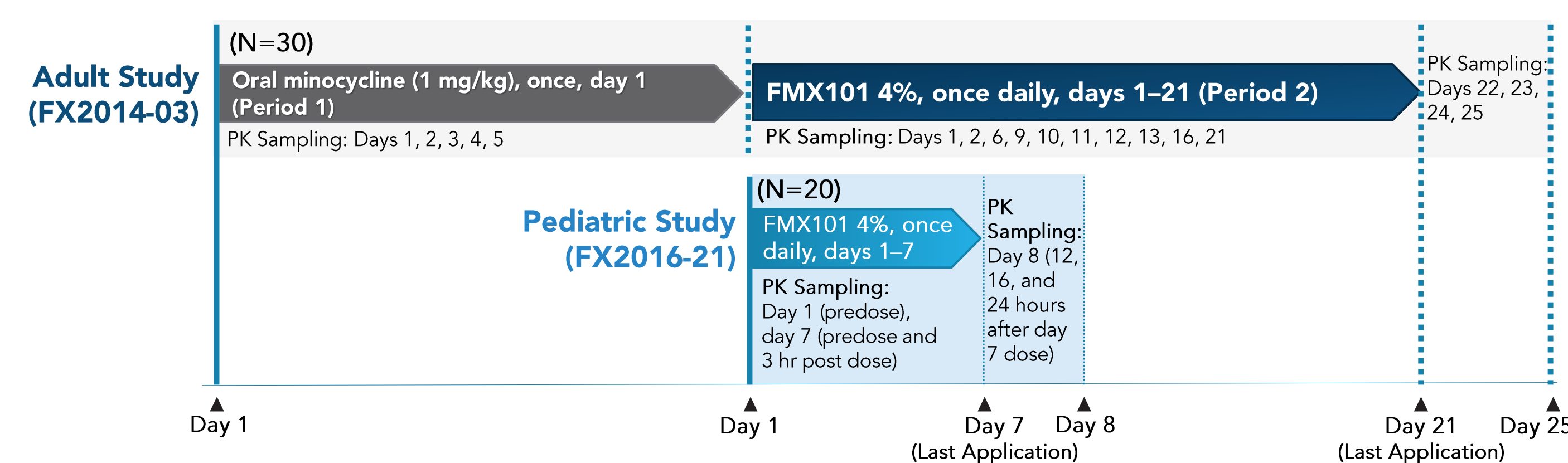


Table 1. Inclusion Criteria and Assessments

| | Adult Study (FX2014-03) | Pediatric Study (FX2016-21) |
|--|---|--|
| Inclusion Criteria | <ul style="list-style-type: none"> Healthy males/females aged 18–35 years Moderate-to-severe facial AV (additionally affecting ≥2 regions of face, neck, upper chest, upper back, or arms) BMI within 18.5–29.9 kg/m²; body weight within 48.0–128.0 kg Not pregnant, lactating, or planning a pregnancy during study | <ul style="list-style-type: none"> Healthy males/females aged 9 years to 16 years, 11 months <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> 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% | <ul style="list-style-type: none"> On day 7, after 3, 12, 16, and 24 hours from last application of FMX101 4% |
| Pharmacokinetic Analyses | <ul style="list-style-type: none"> PK parameters were calculated using noncompartmental methods PK parameters included AUC_{0-inf}, AUC_{0-24h}, AUC_{0-t_{1/2}}, C_{max}, C_{24h}, T_{max}, and accumulation ratio | <ul style="list-style-type: none"> PK parameters were calculated using noncompartmental methods PK parameters included AUC_{0-24h}, C_{max}, and C_{24h} |
| Statistical Analyses | <ul style="list-style-type: none"> Geometric mean was calculated for AUC_{0-inf}, AUC_{0-24h}, AUC_{0-t_{1/2}}, and C_{max} | <ul style="list-style-type: none"> Geometric mean was calculated for AUC_{0-24h} and C_{max} |

AUC_{0-inf}=AUC from 0 to infinity.
 AUC_{0-24h}=AUC during the 24-hour dosing interval.
 AUC_{0-t_{1/2}}=AUC from 0 to time of last determinable concentration.
 C_{24h}=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

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

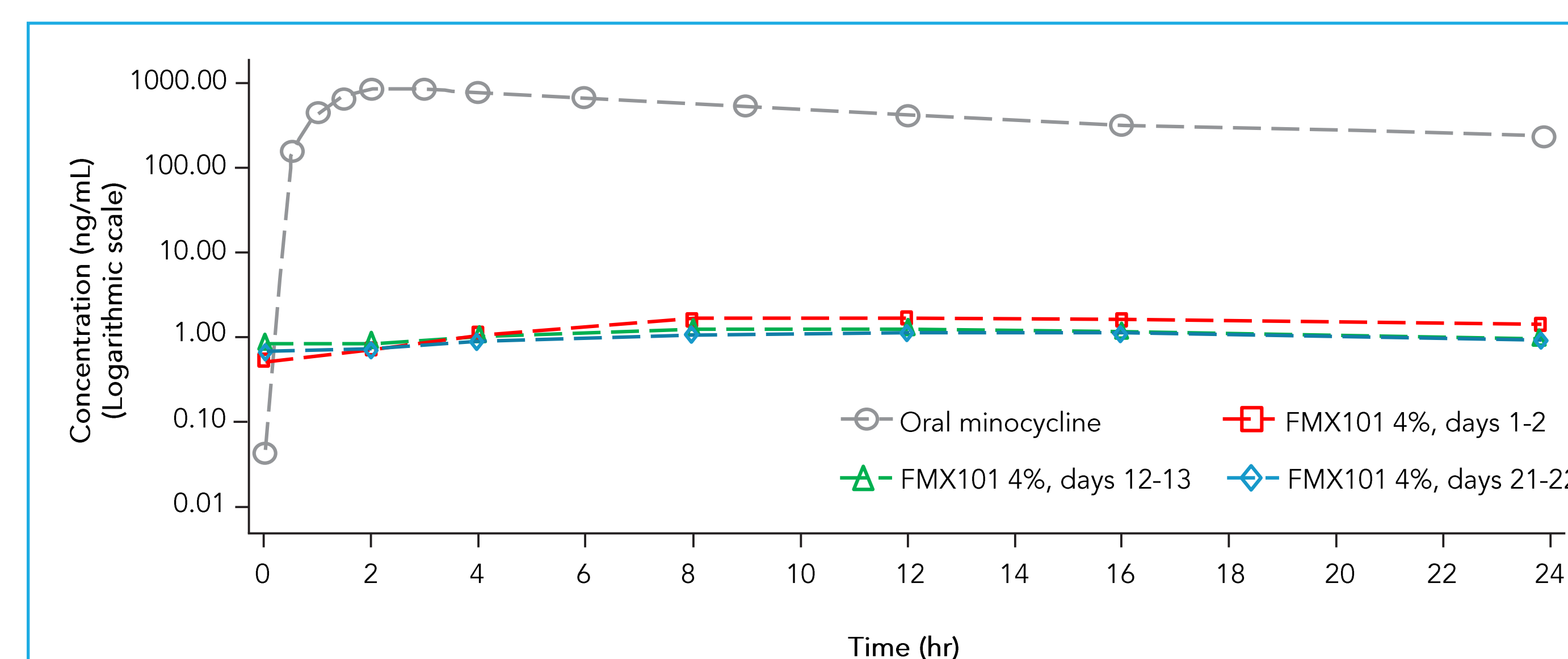
Table 2. Baseline Characteristics

| | 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 | | Geometric LSM Test/Reference Ratio, ^b % (90% CI) | 1/GMR |
|-------------------------------|----|-----------------------------|------------------------|---|-------|
| | | FMX101 4% (Test) | Oral Minocycline (Ref) | | |
| 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 |

^aGeometric mean of oral minocycline and FMX101 4% based on LSM.
^bGeometric LSM ratio and the associated 90% CI were back-transformed point estimates and the associated 90% CI.
^cDay 12 AUC_{0-24h} for FMX101 4% vs AUC_{0-inf} for oral minocycline.
^dDay 21 AUC_{0-24h} for FMX101 4% vs AUC_{0-inf} for oral minocycline.
 CI=confidence interval; LSM=least squares mean; GMR=geometric mean ratio.

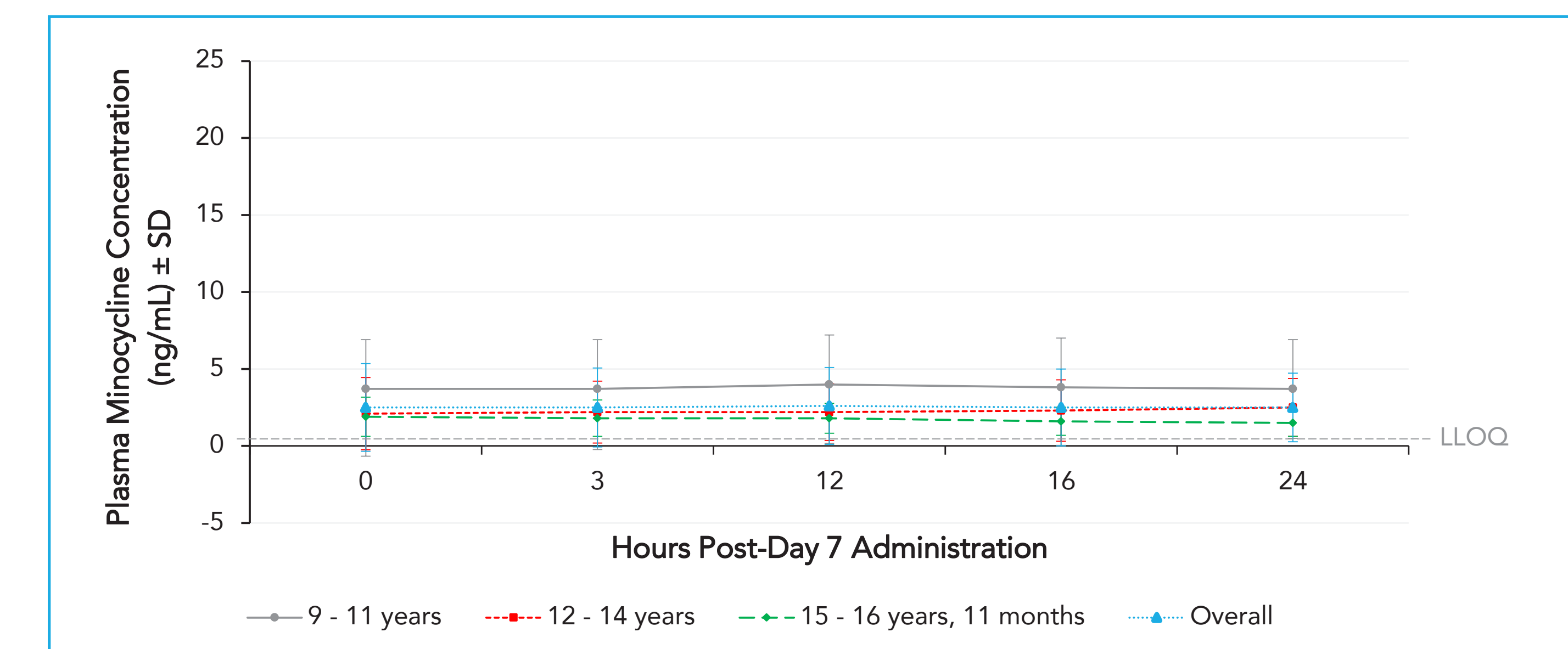
Conclusions

- 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

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) | AUC _{0-24h} (ng*hr/mL) | C _{24h} (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) |

^aMedian (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) | | Pediatric Study (FX2016-21) |
|-------------------------------|-------------------------|------------------|-----------------------------|
| | Oral Minocycline (N=30) | FMX101 4% (N=30) | 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) |

- 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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