CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213690Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	213690
Priority or Standard	Standard
Submit Date(s)	August 2, 2019
Received Date(s)	August 2, 2019
PDUFA Goal Date	June 2, 2020
Division/Office	Division of Dermatology and Dentistry
Review Completion Date	April 30, 2020
Established/Proper Name	Minocycline topical foam, 1.5%
(Proposed) Trade Name	ZILXI
Pharmacologic Class	Rosacea Agents
Code Name	FMX103
Applicant	Foamix Pharmaceuticals Inc.
Dosage Form	Foam
Applicant Proposed Dosing Regimen	Apply to affected areas once daily
Applicant Proposed Indication(s)/Population(s)	Indicated to treat [redacted] (b) (4) rosacea in adults
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	75867005 |Acne rosacea [redacted] (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the treatment of inflammatory lesions [redacted] (b) (4) [redacted] of rosacea in adults
Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)	75867005 |Acne rosacea [redacted] (b) (4)
Recommended Dosing Regimen	Apply a thin layer over all areas of the face once daily. The topical foam should be applied at approximately the same time each day at least 1 hour before bedtime.

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatrics and Maternal Health
DDD = Division of Dermatology and Dentistry

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Signatures

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Glossary

AE	adverse event
ANCOVA	analysis of covariance
AR	adverse reaction
AUC	area under the concentration time curve
BA	bioavailability
BLA	biologics license application
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
COPD	chronic obstructive pulmonary disease
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
ECG	electrocardiogram
ICH	International Conference on Harmonisation
IFU	Instructions for Use
IGA	Investigator Global Assessment
IND	investigational new drug
ITT	intent-to-treat
IV	intravenous
LD	listed drug
LOCF	last observation carried forward
MI	multiple imputation
MRA	magnetic resonance angiogram
MRHD	maximum recommended human dose
NDA	new drug application
NOAEL	no-observed-adverse-effect-level
OCS	Office of Computational Science
OECD	Organisation for Economic Cooperation and Development
OPDP	Office of Prescription Drug Promotion
OSI	Office of Scientific Investigation
PI	prescribing information
PK	pharmacokinetics
PPR	papules and pustules of rosacea
PP	per protocol
PREA	Pediatric Research Equity Act

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PRO	patient-reported outcome
PT	preferred term
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
URTI	upper respiratory tract infection

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1. Executive Summary

1.1. Product Introduction

The Applicant is seeking approval for ZILXI™ (minocycline) topical foam, 1.5% under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The listed drug (LD) is SOLODYN® (minocycline hydrochloride) Extended-Release Tablets (NDA 50808). The Applicant established a clinical bridge between minocycline foam, 1.5% and the LD, and proposes to rely on the Agency's finding of safety for nonclinical toxicology (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) for the LD.

The active ingredient is minocycline, a tetracycline-class antibiotic. Minocycline is currently marketed in the United States in dosage forms including oral capsule and tablet, topical foam, as well as intravenous (IV) injection. The proposed indication is treatment of inflammatory lesions (b) (4) of rosacea in patients 18 years of age and older.

The Agency concluded that the proposed proprietary name, ZILXI, was acceptable from both a promotional and safety perspective under NDA 213690 (Proprietary Name Review by Dr. Valerie S. Vaughan, Division of Medication Error Prevention and Analysis dated March 30, 2020).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled Phase 3 trials (FX2016-11 and FX2016-12) which provided evidence of the effectiveness of minocycline foam, 1.5% for the treatment of inflammatory lesions (b) (4) of rosacea in the target population. Both trials assessed the change from baseline to Week 12 for the following coprimary endpoints:

- Absolute change from baseline in the inflammatory lesion count
- Treatment success at Week 12 defined as an Investigator Global Assessment (IGA) score of 0 ("clear") or 1 ("almost clear"), and at least a two-grade improvement (decrease) from baseline.

Minocycline foam, 1.5% was statistically superior to vehicle (p values ≤0.0218) on the coprimary endpoints in both Phase 3 trials (FX2016-11 and FX2016-12). The Applicant has demonstrated that minocycline foam, 1.5% is effective for its intended use in the target population and has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126(a)(b) to support approval.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant, Foamix Pharmaceuticals, submitted a new drug application (NDA) 213690 for ZILXI™ (minocycline) topical foam, 1.5% under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The proposed indication is treatment of inflammatory lesions [redacted] (b) (4) of rosacea in patients 18 years of age and older. ZILXI is a topical foam formulation of minocycline, a moiety with a well-characterized safety profile. The listed drug (LD) is SOLODYN (minocycline hydrochloride) Extended-Release Tablets (NDA 50808). The Applicant established a clinical bridge between minocycline foam, 1.5% and the LD, and proposes to rely on the Agency's finding of safety for nonclinical toxicology (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) for the LD.

In two Phase 3 (FX2016-11 and FX2016-12), multicenter, randomized, double-blind, vehicle controlled, 2-arm safety and efficacy trials conducted in 1522 subjects ≥18 years of age with moderate to severe papulopustular rosacea, minocycline foam, 1.5% was statistically superior to vehicle (p values ≤0.0218) for the treatment of inflammatory lesions [redacted] (b) (4) of rosacea. The coprimary endpoints for the Phase 3 trials were absolute change from baseline in the inflammatory lesion count at Week 12, and treatment success at Week 12 defined as an IGA score of 0 ("clear") or 1 ("almost clear"), and at least a two-grade improvement (decrease) from baseline at Week 12.

The safety profile for minocycline foam, 1.5% was adequately characterized during the drug development program. Two deaths occurred during the development program; neither was related to treatment with minocycline foam, 1.5%. In the Phase 2 trial (FX2015-10) and Phase 3 trials (FX2016-11 and FX2016-12), (the Phase 2/3 safety population), serious adverse events (SAEs) occurred in 0.5% of subjects treated with minocycline foam, 1.5% and in 1.0% of subjects treated with vehicle. None of the SAEs were related to treatment with minocycline foam, 1.5%. Active assessments of local tolerability in the Phase 3 trials revealed the following results in subjects treated with minocycline foam, 1.5% at Week 12: erythema (89.5%), telangiectasia (79.8%), flushing/blushing (49.5%), dryness/xerosis (28.0%), skin hyperpigmentation (25.3%), itching (23.3%), peeling/desquamation (18.1%), and burning/stinging (16.1%). Investigators characterized the hyperpigmentation as being characteristic of inflammatory and post-inflammatory changes associated with rosacea. Most of the local tolerability findings were mild or moderate in severity and occurred with a similar frequency and severity in subjects treated with the vehicle component of minocycline foam, 1.5%. The most common adverse reaction (AR) was diarrhea, which was reported in 1% of subjects treated with minocycline foam, 1.5% and in 0% of subjects treated with vehicle. The Applicant also submitted long-term safety data from a 40-week open-label extension

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study.

Although systemic exposure from topical administration of minocycline foam, 1.5% was much lower than exposure from SOLODYN® administered orally, the exposure threshold for the events listed in Section 5 (Warnings and Precautions) of labeling for SOLODYN is not definitively known. Therefore, all of the Warnings and Precautions in the labeling for SOLODYN will be included in labeling for ZILXI (minocycline) topical foam, 1.5%.

In summary, rosacea is a chronic disease which may be associated with substantial impairment of quality of life. Minocycline foam, 1.5% provides an additional treatment option for inflammatory lesions (b) (4) associated with rosacea. The available evidence of safety and efficacy supports the approval of ZILXI (minocycline) topical foam, 1.5% for the treatment of inflammatory lesions (b) (4) of rosacea in patients 18 years of age and older. In view of a favorable overall benefit/risk assessment, the review team recommends approval of this product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Rosacea is a chronic dermatological condition that predominantly affects the central region of the face (e.g., cheeks, nose, chin, mid forehead) and onset typically occurs at any time after 30 years of age. It may be characterized by flushing (transient erythema), persistent (nontransient) erythema, telangiectasias, and inflammatory acneiform lesions (papules, pustules). Ocular involvement may occur (e.g., blepharitis, conjunctivitis). The pathways that lead to the development of rosacea are not well understood. Proposed contributing factors include abnormalities in innate immunity, inflammatory reactions to cutaneous microorganisms, ultraviolet damage, and vascular dysfunction. Rosacea may be associated with adverse impacts on emotional, social, and occupational well-being.	Rosacea is a common chronic disorder with a range of disease severities which may significantly impact quality of life.
Current Treatment Options	Currently approved drugs for the treatment of rosacea are indicated specifically for the treatment of persistent (nontransient) facial erythema of rosacea or treatment of inflammatory lesions (papules and pustules) of rosacea. Approved therapies for the treatment of inflammatory lesions (papules and pustules) of rosacea include topical antimicrobials (e.g.	There are a number of FDA-approved products with an acceptable benefit/risk profile for the treatment of inflammatory lesions (b) (6) of rosacea, including

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	metronidazole), ivermectin, and azelaic acid. Doxycycline is the only systemic therapy for inflammatory lesions (b) (4) of rosacea currently approved in the U.S.	doxycycline administered orally. Like doxycycline, minocycline is also a tetracycline class drug. A topical formulation of minocycline effective in the treatment of inflammatory lesions (b) (4) of rosacea with less systemic exposure than oral doxycycline would be a useful addition to the treatment armamentarium.
Benefit	Data from two adequate and well-controlled trials provide substantial evidence of the effectiveness of minocycline foam, 1.5% for the treatment of inflammatory lesions (b) (4) of rosacea. These trials were conducted in 1522 subjects age 18 years or older with moderate to severe papulopustular rosacea. Minocycline foam, 1.5% was statistically superior to vehicle for the coprimary endpoints of absolute change from baseline in the inflammatory lesion count at Week 12, and treatment success at Week 12 defined as an IGA score of 0 ("clear") or 1 ("almost clear"), and at least a two-grade improvement (decrease) from baseline at Week 12. Review of the safety data from the clinical trials identified no new safety signals with minocycline foam, 1.5%, which was well tolerated in all evaluated subgroups.	Minocycline foam, 1.5% provides an effective and safe treatment option for inflammatory lesions (b) (4) of rosacea.
Risk and Risk Management	The primary safety database (Phase 2 trial FX2015-10 and Phase 3 trials FX2016-11 and FX2016-12) included 1087 subjects who were treated with minocycline foam, 1.5%. Two deaths occurred during the development program, neither related to treatment with minocycline foam, 1.5%. There were no SAEs related to treatment with minocycline foam, 1.5%. The most common AR was diarrhea, which was reported in 1% of subjects treated with minocycline foam, 1.5% and in 0% of subjects treated with vehicle. Local tolerability signs and symptoms at Week 12 in subjects	The risks associated with use of minocycline foam, 1.5% appear favorable. Local reactions that occurred were mostly mild or moderate in severity. Prescription labeling, patient labeling,

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treated with minocycline foam, 1.5% included: erythema (89.5%), telangiectasia (79.8%), flushing/blushing (49.5%), dryness/xerosis (28.0%), skin hyperpigmentation (25.3%), itching (23.3%), peeling/desquamation (18.1%), and burning/stinging (16.1%). Investigators characterized the hyperpigmentation as being characteristic of inflammatory and post-inflammatory changes associated with rosacea. Most of the local tolerability findings were mild or moderate in severity and occurred with a similar frequency and severity in subjects treated with the vehicle component of minocycline foam, 1.5%. Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and those identified during product development. No issues require further assessment with a postmarketing requirement or postmarketing commitment. A risk evaluation and mitigation strategy (REMS) is not recommended.	and routine pharmacovigilance are adequate to manage the risks of the product.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	8.2.6
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	8.1.1.1
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

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2. Therapeutic Context

2.1. Analysis of Condition

Rosacea is a chronic dermatological condition that predominantly affects the central region of the face, e.g., cheeks, nose, chin, mid forehead. It may be characterized by flushing (transient erythema), persistent (nontransient) erythema, telangiectasias, and inflammatory acneiform lesions (papules, pustules). Ocular involvement may occur (e.g., blepharitis, conjunctivitis). Rosacea is often characterized by repeated remissions and exacerbations.

Rosacea is a common disorder that is most frequently observed in individuals with lightly pigmented skin (skin phototypes I and II). People of Celtic and Northern European origin appear to have the greatest risk for this disorder. Estimates of the prevalence of rosacea in fair-skinned populations range from 1 to 10 percent. Rosacea has also been diagnosed in Asians, Latin Americans, African-Americans, and Africans. Rosacea is seen more often in women than men, and onset typically occurs at any time after age 30. Rosacea is reported to be rare in children.[1][2]

The pathways that lead to the development of rosacea are not well understood. Proposed contributing factors include abnormalities in innate immunity, inflammatory reactions to cutaneous microorganisms, ultraviolet damage, and vascular dysfunction. Rosacea patients have an increased expression of a variety of genes with roles in both the innate and adaptive immune systems. Microorganisms, such as Demodex folliculorum, Staphylococcus epidermidis, and others may also contribute to the pathogenesis of rosacea by stimulating the innate immune system. Based on the common triggers for rosacea exacerbations, ultraviolet light radiation and the transient receptor potential family of receptors may also play a role in the pathogenesis of rosacea.[3]

In 2002, the National Rosacea Society assembled an expert committee to develop a standard classification system for rosacea. The committee established four distinct subtypes of rosacea: erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea. Since 2002,

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[1] Gallo RL, RD Granstein, S Kang, M Mannis, M Steinhoff, J Tan, D Thiboutot, Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee, J Am Acad Dermatol. 2018 Jan;78(1):148-155.
[2] Dahl MV, Rosacea: Pathogenesis, clinical features, and diagnosis, UpTo Date, Accessed November 19, 2019, https://www.uptodate.com/contents/rosacea-pathogenesis-clinical-features-and-diagnosis?search=Rosacea:%20Pathogenesis,%20clinical%20features,%20and%20diagnosis&source=search_result&selectedTitle=1~108&usage_type=default&display_rank=1
[3] Two, AM, W Wu, RL Gallo, TR Hata, CME Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors, JAAD 2015;72(5):749-758.

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increasing knowledge of the pathophysiology of rosacea has favored the view that rosacea is a consistent multivariate disease process with multiple clinical manifestations rather than distinct subtypes of disease. Following recommendations from an international panel of experts, supporting use of phenotype-based, rather than a subtype-based, approach to the diagnosis and classification of rosacea, the National Rosacea Society Expert Committee released an update supporting a similar approach. The phenotype-based approach describes the individual clinical features of rosacea and divides them into diagnostic, major, and secondary (or minor) features/phenotypes.[1]

Diagnosis of rosacea can be made based upon an assessment for diagnostic, major, and minor phenotypes. At least one diagnostic phenotype or two major phenotypes are required for diagnosis:[1]

- Diagnostic phenotypes
  - Fixed centrofacial erythema in a characteristic pattern that may periodically intensify
  - Phymatous (tissue hypertrophy manifesting as thickened skin with irregular contours) changes
- Major phenotypes
  - Papules and pustules
  - Flushing
  - Telangiectasia
  - Ocular manifestations (e.g., lid margin telangiectases, interpalpebral conjunctival injection, spade-shaped infiltrates in the cornea, scleritis, sclerokeratitis)
- Secondary phenotypes
  - Burning or stinging
  - Edema
  - Dry appearance

Surveys over the last 15 years have documented rosacea's adverse impact on emotional, social, and occupational well-being, including a link to severity. The psychological burden includes depression, anxiety, and worry.[1] Although rosacea's impact on physical health is limited, treatment of rosacea can significantly affect a person's quality of life.[4]

[4] Two, AM, W Wu, RL Gallo, TR Hata, CME Rosacea: part II. Topical and systemic therapies in the treatment of rosacea, JAAD 2015;72(5):761-770.

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2.2. Analysis of Current Treatment Options

Rosacea treatments focus on 3 main categories: patient education, skin care, and pharmacologic/procedural interventions.

If specific triggers or exacerbating factors can be identified, avoiding these triggers, if possible, can be beneficial in controlling an individual's symptoms. Common triggers include wind, hot and cold temperatures, exercise, spicy foods, alcohol, hot drinks, and physical or psychological stress. Avoidance of flushing can be important since easy flushing is a common feature of rosacea.

Proper skin care plays a pivotal role in maintaining remission and alleviating the symptoms of rosacea. Rosacea skin has been shown to have increased transepidermal water loss indicative of defective barrier functions, and therefore moisturizers are important to help restore this barrier and facilitate remission of rosacea exacerbations. Daily sun protection is also important in skin care. By blocking ultraviolet light, sunscreens decrease LL-37 production and the subsequent production of reactive oxygen species that can trigger rosacea.

Topical drug products approved by the US Food and Drug Administration for rosacea include azelaic acid gel/foam, 15%, metronidazole cream /gel /lotion 0.75% & gel 1%, ivermectin cream, 1%, oxymetazoline HCl cream, 1%, and brimonidine gel, 0.33%.

Systemic therapies approved by the US Food and Drug Administration for the treatment of inflammatory lesions (b) (4) of rosacea include only doxycycline 40 mg capsules.

Table 1: FDA-Approved Products for Rosacea

NDA Number	Trade Name	Generic Name	Sponsor	Approval Date	Indication
020531	METROCREAM (metronidazole topical cream)	Metronidazole cream, 0.75%	Galderma	09/20/1995	Inflammatory papules and pustules of rosacea
020743	NORITATE (metronidazole cream) Cream, 1%	Metronidazole cream, 1%	Valeant International Bermuda	09/26/1997	Inflammatory lesions and erythema of rosacea
019737	METROGEL (metronidazole) Gel, 0.75%	Metronidazole 0.75%	Galderma	11/22/1988	Inflammatory papules and pustules of rosacea
020901	MetroLotion (metronidazole lotion) Topical Lotion, 0.75%	Metronidazole 0.75%	Galderma	11/24/1998	Inflammatory papules and pustules of rosacea
021470	FINACEA (azaleic acid) Gel, 15%	Azaleic acid gel, 15%	Berlex Laboratories, Inc.	12/24/2002	Inflammatory papules and pustules of mild to moderate rosacea

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NDA Number	Trade Name	Generic Name	Sponsor	Approval Date	Indication
021789	METROGEL (metronidazole) Gel, 1%	Metronidazole gel, 1%	Galderma	06/30/2005	Inflammatory lesions of rosacea
050805	ORACEA (doxycycline) capsules	Doxycycline capsules, 40 mg	Galderma	05/26/2006	Inflammatory lesions (papules and pustules) of rosacea
204708	MIRVASO (brimonidine) topical gel, 0.33%	Brimonidine topical gel, 0.33%	Galderma	08/23/2013	Persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older
206255	SOOLANTRA (ivermectin) cream, 1%	Ivermectin cream, 1.0%	Galderma	12/19/2014	Inflammatory lesions of rosacea
207071	FINACEA (azaleic acid) Foam, 15%	Azaleic acid foam, 15%	Bayer Healthcare Pharmaceuticals, Inc.	7/29/2015	Inflammatory papules and pustules of mild to moderate rosacea
208552	RHOFADE (oxymetazoline HCl) cream, 1%	Oxymetazoline HCl cream, 1%	Allergan	1/18/2017	Persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older

Source: Drugs@FDA, accessed 1/7/2020

Table 2: Additional Information for Representative Examples of FDA-Approved Products for Rosacea

Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From labeling	Important Safety and Tolerability Issues
For treatment of inflammatory lesions of rosacea				
METROGEL (metronidazole) Gel, 1%, NDA 021789 (2005)	Inflammatory lesions of rosacea	Once daily to affected areas	1, 10-week R, VC trial in 746 subjects Active vs vehicle IGA: 38% vs 27% Inflam: 51% vs 33%	AR: contact dermatitis W&P: Peripheral neuropathy, irritant and allergic contact dermatitis
FINACEA (azelaic acid) Foam, 1% NDA 207071 (2015)	Inflammatory papules and pustules of mild to moderate	Twice daily to entire facial area	2, 12-week R, DB, VC trials in 513 subjects with papulopustular rosacea. Active vs vehicle 1) IGA: 32% vs 23 Inflam:13% vs 10% 2) IGA: 43% vs 33 Inflam: 13% vs 10%	AR: application site pain & pruritus, W&P: hypopigmentation, eye irritation, flammable propellant

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Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From labeling	Important Safety and Tolerability Issues
SOOLANTRA (ivermectin) cream, 1% NDA 206255 (2014)	Inflammatory lesions of rosacea	Once daily to affected areas	2, 12-week R, DB, VC trials in 1371 subjects with moderate to severe rosacea Active vs vehicle 1) IGA:38% vs 12% Inflam: 65% vs 42% 2) IGA:40% vs 19% Inflam:66% vs 43%	AR: skin burning sensation and skin irritation W&P: none
For treatment of persistent (nontransient) facial erythema of rosacea				
MIRVASO (brimonidine) topical gel, 0.33% NDA 204708 (2013)	Persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older	Pea-sized amount once daily to each of the five areas of the face: central forehead, chin, nose, each cheek	2, 4-week R, DB, VC trials in 553 subjects with moderate to severe, persistent (nontransient) facial erythema of rosacea Active vs vehicle Success 1) CEA & PSA: Hour 3: 31% vs 11 Hour 6: 30% vs 10 Hour 9: 26% vs 10 Hour 12: 23% vs 9 2) CEA & PSA: Hour 3: 25% vs 9 Hour 6: 25% vs 9 Hour 9: 18% vs 11 Hour 12: 22% vs 10	AR: erythema, flushing W&P: potentiation of vascular insufficiency, can lower blood pressure – use with caution in patients with severe or unstable or uncontrolled cardiovascular disease
RHOFADE (oxymetalozine hydrochloride) cream, 1% NDA 208552 (2017)	Persistent facial erythema associated with rosacea in adults	Pea-sized amount, once daily in a thin layer to cover the entire face (forehead, nose, each cheek, and chin)	2, 29-day R, DB, VC trials in 885 subjects with moderate to severe persistent erythema of rosacea Active vs vehicle Success: 1) CEA & SSA: Hour 3: 12% vs 6 Hour 6: 16% vs 8 Hour 9: 18% vs 6 Hour 12: 15% vs 6 2) CEA & SSA: Hour 3: 14% vs 7 Hour 6: 13% vs 5 Hour 9: 16% vs 9 Hour 12: 12% vs 6	AR: application site dermatitis W&P: may impact blood pressure (use with caution in patients with severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension), used with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, thromboangiitis obliterans, scleroderma, or

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Product(s) Name/ Year of Approval	Indication	Dosing/ Administration	Efficacy Information From labeling	Important Safety and Tolerability Issues
				Sjögren's syndrome, may increase the risk of angle closure glaucoma in patients with narrow-angle glaucoma
Oral product for treatment of inflammatory lesions of rosacea				
ORACEA(doxycycline) capsules NDA 050805 (2006)	treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients	Capsule (40 mg) once daily	2, 16-week R, DB, PC trials in 537 subjects with rosacea (10 to 40 papules and pustules and 2 or fewer nodules) <u>Active vs vehicle</u> 1) IGA: 31% vs 19 Inflam: 12% vs 6% 2) IGA: 15% vs 6% Inflam: 10% vs 4%	AR: upper abdominal pain, diarrhea, hypertension, LDH increase W&P: class labeling; teratogenic effects, pseudomonas colitis, may increase BUN, photosensitivity, tissue hyperpigmentation, pseudotumor cerebri

Abbreviations: AR = adverse reaction; W&P = Warnings and Precautions; R = randomized; DB = double-blind; VC = vehicle controlled; IGA = Investigator Global Assessment; Inflam = inflammatory; CEA = Clinical (or Clinician) Erythema Score; PSA = Patient Self Assessment Scale; SSA = Subject Self-Assessment scale; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; PC = placebo-controlled
Source: Approved labeling for drug products listed

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Because minocycline foam, 1.5% is not currently marketed in the United States, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed minocycline foam, 1.5%, under investigational new drug (IND) application 132239 using the 505(b)(2) regulatory pathway. The Applicant selected SOLODYN (minocycline HCl) Extended-Release Tablets (NDA 50808) as the LD and proposed to establish a clinical bridge to the LD in order to rely upon the Agency's findings of safety for nonclinical toxicology (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) for the LD.

A Pre-IND meeting occurred on December 12, 2016. The Agency recommended that the Applicant conduct a maximal use pharmacokinetics (PK) trial; however, the comparator listed drug (SOLODYN) would not be needed and the Applicant could do a cross-study comparison and use SOLODYN PK data from study FX2014-03. (The minocycline foam, 1.5% is anticipated to have a lower bioavailability (BA) compared to the LD SOLODYN, because the relative BA study

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with minocycline foam, 4% showed that the foam formulation had 650-770-fold lower minocycline exposure compared to the LD).

Previous human experience included conduct of a non-IND Phase 2 dose-ranging trial (FX2015-10) that evaluated two doses (1.5% and 3.0%) of minocycline in a foam formulation for the treatment of inflammatory lesions (b) (4) of rosacea in adults. Based on the results of this trial, the Applicant selected the 1.5% dose for the pivotal Phase 3 trials. The Applicant was advised at the Pre-IND meeting that the results of the Phase 2 trial did not show a dose-response and, therefore it was not clear whether the Applicant selected the dose/regimen of their proposed product most likely to succeed in Phase 3. Also, at the Pre-IND meeting, the Applicant was advised that the Physician Global Assessment scale should represent a static evaluation of global severity with a limited number of categories which represent clinically meaningful gradations of disease, and not include lesion counts. The Applicant was further advised that local safety assessment should include active assessment of local signs and symptoms (e.g., erythema, dryness, pigmentation, peeling, and itching) using appropriate scales.

Regarding the possibility of establishing safety and efficacy with a single Phase 3 clinical trial, the Applicant was informed at the pre-IND meeting that, in general, to establish safety and efficacy of the proposed drug product, two adequate and well-controlled clinical trials were recommended. For establishing an efficacy claim, the trial needed to be well designed and include a prespecified statistical analysis plan. Regarding the size of the safety database needed, for the proposed indication in the target population, the Applicant was referred to the International Conference on Harmonisation guideline for industry, E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions. The Applicant was also informed that provocative studies to evaluate dermal safety of topical drug products re recommended prior to marketing.

The Applicant opened the IND on February 28, 2017 by submitting non- Special Protocol Assessment Phase 3 protocols for two identical trials FX2016-11 and FX2016-12 titled as follows: "A Randomized, Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of FMX103 1.5% Topical Foam Compared to Vehicle in the Treatment of Facial Papulopustular Rosacea." The protocol described a trial in which qualified subjects with "moderate-to-severe (according to IGA score) facial papulopustular rosacea" were to be randomized in a 2:1 ratio to receive either FMX103 minocycline foam, 1.5% or vehicle foam. Efficacy evaluations (inflammatory lesion counts and IGA score was to be performed at Weeks 4, 8, and 12 during the study. The coprimary efficacy endpoints were: absolute change in inflammatory lesion count at Week 12 compared to baseline and IGA success at Week 12 where success was defined as a score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. The Study May Proceed letter, issued April 24, 2017, principally included statistical comments; a recommendation that randomization should be stratified by investigational site, a statement that the protocol should prespecify the complete criteria for inclusion in the per-protocol population, and a statement that complete details of the multiple imputation (MI) procedure be fully prespecified in the statistical analysis plan.

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Refer to Pediatrics and Assessment of Effects on Growth in Section 8.2.9 for a discussion of the pediatric development plan for minocycline foam, 1.5%.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. The sites were selected for inspection by Office of Scientific Investigations based on number of enrolled subjects, site efficacy, and prior inspectional history. The clinical inspection summary (review by Cheryl Grandinetti, Pharm.D. dated March 12, 2020) included the following results, which are summarized in the table below:

Table 3: Site Inspection Results

Site Number, Name, and Address	Protocol ID	Number of Subjects	Classification
Deirdre Hooper, MD Site #115 DelRicht Research 3525 Prytania Street, Suite 308 and 501 New Orleans, LA 70115	FX2016-11	59	NAI
Martin Zaiac, MD Site #144 Sweet Hope Research Specialty, Inc. 14160 Palmetto Frontage Road, Suite 100 Miami Lakes, FL 33016	FX2016-11	49	NAI
Kim Abson, MD Site #203 The Polyclinic Madison Center 904 7th Avenue Seattle, WA 98104	FX2016-12	21	NAI (1 data discrepancy noted; considered minor and unlikely to impact overall efficacy results)
Steven Kempers, MD Site #232 Minnesota Clinical Study Center 7205 University Avenue NE Fridley, MN 55432	FX2016-12	24	VAI (see discussion below)

Source: Reviewer's Table
Abbreviation: NAI = no action indicated; VAI = Voluntary Action Indicated

At Site 232 (Stephen Kempers, MD), four subjects had severe erythema at Screening and thus met exclusion criteria and should have been screen failures. These four protocol deviations were reported to the Agency in data listings. The Office of Scientific Investigations sent a Voluntary Action Indicated letter to Dr. Kempers on 3/20/2020.

The review team concluded that the conduct of the trials appears to be adequate and the data generated appears to be acceptable to support the use of this product for the proposed

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indication. Refer to the Clinical Inspection Summary by Cheryl Grandinetti, Pharm.D. for further information regarding findings from the Clinical Site Inspections.

4.2. Product Quality

Foamix Pharmaceuticals Inc. has submitted this 505(b)(2) new drug application for ZILXI (minocycline) topical foam, 1.5%. The proposed indication is treatment of (b) (4) rosacea in adults.

- The Applicant selected SOLODYN (minocycline hydrochloride) Extended-Release as the LD.
- The Applicant has provided sufficient chemistry, manufacturing, and control information to assure the identity, purity, strength, and quality of the drug substance and the drug product.
- Labels/labeling issues have been satisfactorily addressed.
- The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment is granted.

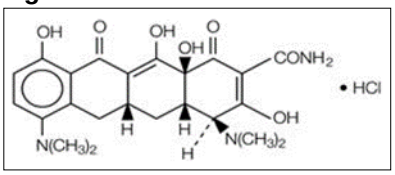
Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is recommended for approval with expiration dating period of 18 months.

<u>Drug Substance</u>

The active moiety, minocycline, is a semi-synthetic derivative of tetracycline antibiotic that has been approved as its hydrochloride salt, minocycline hydrochloride, since 1971. Oral drug products containing minocycline have shown to have antibacterial and anti-inflammatory effects. Minocycline is a compendial drug substance and since its original approval, multiple brand name and generic drug products containing minocycline have been approved and are currently being marketed as capsules, tablets, extended-release tablets, oral suspensions, injections, and periodontal systems.

Minocycline hydrochloride has the molecular formula of $C_{23}H_{27}N_3O_7 \cdot HCl$, the molecular weight of 493.94, and the molecular structure below:

Figure 1: Molecular Structure of Minocycline Hydrochloride



Micronized minocycline hydrochloride for this application is manufactured and supplied by (b) (4) in accordance with current good manufacturing practices (cGMP) and in compliance with the USP and the European Pharmacopoeia Monographs. It is tested against an adequate specification that assures the identity, strength, purity, and quality of drug substance at release and throughout its proposed

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retest date of [redacted] (b) (4). The information regarding the manufacture of micronized minocycline hydrochloride by [redacted] (b) (4) is provided in DMF [redacted] (b) (4) and the information regarding the manufacture of micronized minocycline hydrochloride [redacted] (b) (4). is provided in DMF [redacted] (b) (4). Both DMF [redacted] (b) (4) and DMF [redacted] (b) (4) have been reviewed and found to be adequate to support this new drug application.

Drug Product

The drug product, ZILXI (minocycline) topical foam, 1.5% is produced as a non-aqueous, oil-based, suspension pre-formulation containing 16 mg/g of micronized minocycline hydrochloride equivalent to 15 mg/g minocycline, filled into aluminum canisters with the propellant, [redacted] (b) (4) that facilitates delivery of the product as aerosolized foam, for topical administration. The physician sample canisters deliver 7 g of the topical foam and the commercial drug product canisters deliver 30 g of the topical foam.

The pre-foam formulation also contains soybean oil, coconut oil, light mineral oil, cyclomethicone 5, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, and docosanol [redacted] (b) (4), as inactive ingredients, [redacted] (b) (4) The inactive ingredients used in the composition of the drug product are all compendial materials or materials currently approved (2019) for use in AMZEEQ (minocycline) topical foam, 4%.

The drug product is manufactured and packaged by the contract manufacturer, ASM Aerosol-Service AG, Switzerland, for Foamix Pharmaceuticals, Inc. in accordance with cGMP requirements. It is tested and released according to testing and acceptance criteria for all physical and chemical attributes essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 18 months.

4.3. Clinical Microbiology

Minocycline is a tetracycline-class antibiotic; however, the mechanism of action of minocycline for the treatment of inflammatory lesions [redacted] (b) (4) of rosacea is unknown. The Applicant did not conduct any in vivo microbiology studies during clinical trials with minocycline foam, 1.5%. Therefore, we will not include Section 12.4 (Microbiology) in product labeling. The following statement will be included in Section 1 (Indications and Usage) in Product labeling:

Limitations of Use

This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, ZILXI should be used only as indicated *[see Warnings and Precautions (*5.14*)]*.

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4.4. Devices and Companion Diagnostic Issues

This section is not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted a 505(b)(2) application for ZILXI (minocycline) topical foam, 1.5% for the treatment of inflammatory lesions of rosacea in adults, using SOLODYN (minocycline hydrochloride) Extended-Release Tablets as the LD. SOLODYN has been approved for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older under NDA 50808 since 2006.

The Applicant has established an adequate clinical bridge to the LD SOLODYN. Refer to the Clinical Pharmacology section of this review for details. The Applicant is relying on the Agency's finding of safety for the LD. The Applicant intends to rely on the nonclinical information from the approved labeling for the LD that includes fertility and reproduction, embryofetal development, genetic toxicity, and carcinogenicity. The toxicity profile of minocycline is well-characterized and typical for the tetracycline drug class.

The Applicant conducted a pivotal 39-week repeat dose dermal toxicity study in minipigs with minocycline foams, 4%, 8%, and 16% to support their other minocycline topical drug product, AMZEEQ (minocycline) topical foam, 4%, which has been approved in 2019 for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older under NDA 212379. Minocycline foam, 1.5% has the identical formulation as AMZEEQ except that the concentration of minocycline is 2.7-fold lower with a compensatory increase in the amount of light mineral oil. The Applicant used the toxicity data from this 39-week dermal toxicity study in minipigs to support the safety of Minocycline foam, 1.5%.

In the pivotal 39-week dermal toxicity study in minipigs, minocycline foams, 4%, 8%, and 16% (corresponding to 10, 20, and 40 mg/kg/day minocycline) were well-tolerated. No test article-related adverse effects were noted. The no-observed-adverse-effect-level (NOAEL) was 40 mg/kg/day (minocycline foam, 16% once daily at 0.25 g/kg/day on a ~10% body surface area for 39 weeks). The area under the concentration time curve (AUC) value associated with this NOAEL (1160 hr*ng/mL) is 50 times the maximum recommended human dose (MRHD) of minocycline foam, 1.5% (based on AUC comparison). A dermal carcinogenicity study was not conducted with minocycline foam since no preneoplastic and hyperplastic changes were reported in the skin or any other tissues of the animals in the 39-week dermal toxicity study in minipigs.

Minocycline foam, 1.5% does not contain any novel excipients. There are no issues with impurities in the drug substance/product from a Pharmacology/Toxicology perspective. Safety of impurities has been adequately addressed under NDA 212379 for AMZEEQ.

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Minocycline foam, 1.5% is approvable for the treatment of inflammatory lesions of rosacea in adults from a Pharmacology/Toxicology perspective. There are no recommended nonclinical postmarketing commitments / postmarketing requirements for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

This NDA makes reference to the following DMFs.

DMF (b) (4): minocycline hydrochloride micronized, active, 01/16/2015.

DMF (b) (4): minocycline hydrochloride (b) (4) micronized, active, 12/06/2018.

The Applicant intends to rely on the Agency's findings of safety for the LD SOLODYN (NDA 50808).

NDA 212379: AMZEEQ (minocycline) topical foam, 4% approved for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older on 10/16/2019.

The following nonclinical studies were reviewed under INDs 122770 or 132239. A summary of these studies is provided below. The code name for minocycline foam, 1.5% is FMX103 Foam. FMX101 Foam is the code name for AMZEEQ (minocycline) topical foam, 4%.

5.3. Pharmacology

Primary Pharmacology

Minocycline inhibits the growth of certain species of bacteria through inhibition of protein synthesis by blocking aminoacyl-tRNA binding to the mRNA-ribosome complex.

The mechanism of action of ZILXI for the treatment of inflammatory lesions of rosacea is unknown.

The pharmacodynamics of ZILXI for the treatment of inflammatory lesions of rosacea are unknown.

Secondary Pharmacology

None.

Safety Pharmacology

The Applicant did not submit any safety pharmacology studies. Adequate safety pharmacology studies were conducted to support approval of the LD (SOLODYN).

5.4. ADME/PK

The toxicokinetics of minocycline in plasma were determined in a 3-, 12- and 39-week repeat dose toxicity study in minipigs conducted with minocycline foam. A summary of these

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toxicokinetics data is provided below. FMX101 Foam is the code name for AMZEEQ (minocycline) topical foam, 4%.

Type of Study TK data from general toxicology studies	Major Findings
A 3-Week Dermal Toxicity Study of FMX-101 Foam Followed by a 2-Week Recovery Period in Hanford Minipigs (Study # S12919)	<u>Day 1</u> C_{max}: 3.7% (3.7 mg/kg/day): N/A 7.4% (7.4 mg/kg/day): 1.8 ng/mL 11.2% (28 mg/kg/day): 0.9 ng/mL T_{max}: 3.7% (3.7 mg/kg/day): N/A 7.4% (7.4 mg/kg/day): 7.2 hour 11.2% (28 mg/kg/day): 15.9 hour $AUC_{0\text{-}last}$: 3.7% (3.7 mg/kg/day): N/A 7.4% (7.4 mg/kg/day: N/A 11.2% (28 mg/kg/day): 14.4 ng·hr/mL <u>Day 21</u> C_{max}: 3.7% (3.7 mg/kg/day): 1.3 ng/mL 7.4% (7.4 mg/kg/day): 4.6 ng/mL 11.2% (28 mg/kg/day): 22.4 ng/mL T_{max}: 3.7% (3.7 mg/kg/day): 5.0 hour 7.4% (7.4 mg/kg/day): 3.0 hour 11.2% (28 mg/kg/day): 3.8 hour $AUC_{0\text{-}last}$: 3.7% (3.7 mg/kg/day): 18.2 ng·hr/mL 7.4% (7.4 mg/kg/day): 70.8 ng·hr/mL 11.2% (28 mg/kg/day): 326 ng·hr/mL *Accumulation:* Systemic exposure increased across all three groups after 21 consecutive once daily dermal doses of minocycline foam. *Dose proportionality:* Systemic exposure increased roughly dose-proportionally.
A 12-Week Dermal Toxicity Study of FMX-101 Foam with 4-Week Recovery in Hanford Minipigs (Study # S12917)	<u>Day 1</u> C_{max}: 3.7% (9.3 mg/kg/day): 1.1 ng/mL 7.4% (18.5 mg/kg/day): 1.4 ng/mL 11.2% (37 mg/kg/day): 3.3 ng/mL T_{max}: 3.7% (9.3 mg/kg/day): 5.8 hour

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Type of Study TK data from general toxicology studies	Major Findings
	7.4% (18.5 mg/kg/day): 6.0 hour 11.2% (37 mg/kg/day): 9.7 hour *$AUC_{0\text{-}last}$:* 3.7% (9.3 mg/kg/day): 8.6 ng·hr/mL 7.4% (18.5 mg/kg/day): 12.8 ng·hr/mL 11.2% (37 mg/kg/day): 40.7 ng·hr/mL *Dose proportionality:* Systemic exposure increased roughly dose-proportionally. <u>Day 84</u> *C_{max}:* 3.7% (9.3 mg/kg/day): 16.1 ng/mL 7.4% (18.5 mg/kg/day): 39.3 ng/mL 11.2% (37 mg/kg/day): 34.3 ng/mL *T_{max}:* 3.7% (9.3 mg/kg/day): 2.5 hour 7.4% (18.5 mg/kg/day): 3.0 hour 11.2% (37 mg/kg/day): 4.5 hour *$AUC_{0\text{-}last}$:* 3.7% (9.3 mg/kg/day): 170 ng·hr/mL 7.4% (18.5 mg/kg/day): 346 ng·hr/mL 11.2% (37 mg/kg/day): 394 ng·hr/mL *Accumulation:* Systemic exposure increased across all three groups after 84 consecutive once daily dermal doses of minocycline foam. *Dose proportionality:* Systemic exposure increased roughly dose-proportionally between low dose and mid dose groups, but not between mid dose and high dose groups.
A 39-Week Dermal Toxicity Study of FMX-101 Foam With 4-Week Recovery in Hanford Minipigs (Study # S1314)	<u>Week 4</u> *C_{max}:* 4% (10 mg/kg/day): 24.1 ng/mL 8% (20 mg/kg/day): 26.2 ng/mL 16% (40 mg/kg/day): 105 ng/mL *T_{max}:* 4% (10 mg/kg/day): 2.1 hour 8% (20 mg/kg/day): 7.4 hour 16% (40 mg/kg/day): 0.1 hour *$AUC_{0\text{-}last}$:* 4% (10 mg/kg/day): 214 ng·hr/mL 8% (20 mg/kg/day): 346 ng·hr/mL 16% (40 mg/kg/day): 1060 ng·hr/mL

Reference ID: 4616286

Type of Study TK data from general toxicology studies	Major Findings
	Dose proportionality: Systemic exposure increased roughly dose-proportionally. <u>Week 20</u> C_{max}: 4% (10 mg/kg/day): 41.2 ng/mL 8% (20 mg/kg/day): 35.3 ng/mL 16% (40 mg/kg/day): 88.4 ng/mL T_{max}: 4% (10 mg/kg/day): 3.0 hour 8% (20 mg/kg/day): 4.8 hour 16% (40 mg/kg/day): 2.4 hour $AUC_{0\text{-}last}$: 4% (10 mg/kg/day): 409 ng·hr/mL 8% (20 mg/kg/day): 418 ng·hr/mL 16% (40 mg/kg/day): 896 ng·hr/mL *Accumulation:* No significant systemic accumulation from Week 4 to Week 20; ratios of Week 20 $AUC_{0\text{-}last}$ to Week 4 $AUC_{0\text{-}last}$ were 1.9, 1.2, and 0.8 for 10, 20, and 40 mg/kg/day, respectively. *Dose proportionality:* Systemic exposure increased less than roughly dose-proportionally. <u>Week 39</u> C_{max}: 4% (10 mg/kg/day): 32.4 ng/mL 8% (20 mg/kg/day): 22.6 ng/mL 16% (40 mg/kg/day): 82.5 ng/mL T_{max}: 4% (10 mg/kg/day): 2.0 hour 8% (20 mg/kg/day): 3.8 hour 16% (40 mg/kg/day): 2.0 hour $AUC_{0\text{-}last}$: 4% (10 mg/kg/day): 388 ng·hr/mL 8% (20 mg/kg/day): 351 ng·hr/mL 16% (40 mg/kg/day): 1160 ng·hr/mL *Accumulation:* No evidence of systemic accumulation after Week 20. *Dose proportionality:* Systemic exposure increased less than dose-proportionally.

The Applicant conducted one clinical PK study with minocycline foam, 1.5% in adults with moderate to severe facial papulopustular rosacea and one clinical PK study with AMZEEQ

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(minocycline) topical foam, 4%, and the LD, SOLODYN tablets, in adults with moderate to severe acne vulgaris. The relative bioavailability comparison was conducted based on the data from these two clinical PK studies. It is determined that the Applicant has established an adequate clinical bridge to the LD. Refer to the Clinical Pharmacology section of this review for details.

5.5. Toxicology

5.5.1. General Toxicology

Study 1 A 3-Week Dermal Toxicity Study of FMX-101 Foam Followed by a 2-Week Recovery Period in Hanford Minipigs (Study # S12919)

In a 3-week repeat dose study, minocycline foam, 3.7%, 7.4%, and 11.2% were topically administered (nonoccluded) to Hanford minipigs once daily at dose volume of 0.1 or 0.25 g/kg on a ~10% body surface area (corresponding to 3.7, 7.4, and 28 mg/kg/day minocycline, respectively). No test article-related adverse effects on clinical observation, electrocardiogram (ECG), ophthalmology, food consumption, body weight, clinical pathology, macroscopic pathology, organ weights, or histopathology were noted. Based on the results from this study, the NOAEL for both local and systemic toxicity was 11.2% minocycline foam (28 mg/kg/day). The C_{max} and $AUC_{0\text{-last}}$ values associated with this NOAEL were 22.4 ng/mL and 326 hr*ng/mL, respectively.

Study 2 A 12-Week Dermal Toxicity Study of FMX-101 Foam With 4-Week Recovery in Hanford Minipigs (Study # S12917)

In a 12-week repeat dose study, minocycline foam, 3.7%, 7.4%, and 14.9% were topically administered (nonoccluded) to Hanford minipigs once daily at dose volume of 0.25 g/kg on a ~10% body surface area (corresponding to 9.25, 18.5, and 37.25 mg/kg/day minocycline, respectively). No test article-related adverse effects on clinical observation, ECG, ophthalmology, food consumption, body weight, clinical pathology, macroscopic pathology, organ weights, or histopathology were noted. Based on the results from this study, the NOAEL for both local and systemic toxicity was 14.9% once daily at dose volume of 0.25 g/kg or 37.25 mg/kg/day. The C_{max} and $AUC_{0\text{-last}}$ values associated with this NOAEL were 34.3 ng/mL and 394 hr*ng/mL, respectively.

Study 3 A 39-Week Dermal Toxicity Study of FMX-101 Foam With 4-Week Recovery in Hanford Minipigs (Study # S13145)

In a 39-week repeat dose study, minocycline foam, 4%, 8%, and 16% were topically administered (nonoccluded) to Hanford minipigs once daily at dose volume of 0.25 g/kg/day on a ~10% body surface area (corresponding to 10, 20, and 40 mg/kg/day minocycline, respectively). No test article-related adverse effects on clinical observation, ECG, ophthalmology, food consumption, body weight, clinical pathology, macroscopic pathology, organ weights or histopathology were noted. No preneoplastic, hyperplastic or other histological changes were reported in the skin or any other tissue of the animals. Clinical observations showed the most common dose site findings from week 4 through the end of the

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study included patchy erythema, scabbing, discoloration (staining), rash, and small papules. These findings were not considered to be test article-related, as they were more commonly noted in the vehicle control treated animals. Overall, it was demonstrated that there were no test article-related effects including at the dose sites. Based on the results from this study, the NOAEL for both local and systemic toxicity was 16% minocycline foam (40 mg/kg/day). The C_{max} and AUC_{last} values associated with this NOAEL were 82.5 ng/mL and 1160 hr*ng/mL, respectively. The AUC value associated with this NOAEL (1160 hr*ng/mL) is 50 times the MRHD of minocycline foam, 1.5% (based on AUC comparison).

5.5.2. Genetic Toxicology

The following genetic toxicology information is included in the SOLODYN labeling and the same information will be conveyed in Section 13.1 of the ZILXI labeling.

Minocycline was not mutagenic in vitro in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.

5.5.3. Carcinogenicity

A waiver request for conduct of a dermal carcinogenicity study with AMZEEQ was granted based on the results from a 39-week dermal toxicity study with minocycline foam in minipigs. No preneoplastic and or hyperplastic changes were reported in the skin in the 39-week dermal toxicology study in minipigs. This reviewer agrees with the Applicant that this waiver is applicable to ZILXI because ZILXI has the identical formulation except that the concentration of minocycline is 2.7-fold lower with a compensatory increase in the amount of light mineral oil.

The following carcinogenicity information is included in the SOLODYN labeling and the same information will be conveyed in Section 13.1 of the ZILXI labeling.

In a carcinogenicity study in which minocycline HCl was orally administered to male and female rats once daily for up to 104 weeks at dosages up to 200 mg/kg/day, minocycline HCl was associated in both genders with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas, and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a carcinogenicity study in which minocycline HCl was orally administered to male and female mice once daily for up to 104 weeks at dosages up to 150 mg/kg/day, exposure to minocycline HCl did not result in a significantly increased incidence of neoplasms in either males or females.

5.5.4. Reproductive and Developmental Toxicology

The following reproductive and developmental toxicology information is included in the SOLODYN labeling and the same information will be conveyed in Section 8.1 of the ZILXI labeling.

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SOLODYN should not be used during pregnancy. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and stop treatment immediately.

There are no adequate and well-controlled studies on the use of minocycline in pregnant women. Minocycline, like other tetracycline-class drugs, crosses the placenta and may cause fetal harm when administered to a pregnant woman.

Rare spontaneous reports of congenital anomalies including limb reduction have been reported with minocycline use in pregnancy in post-marketing experience. Only limited information is available regarding these reports; therefore, no conclusion on causal association can be established.

Minocycline induced skeletal malformations (bent limb bones) in fetuses when administered to pregnant rats and rabbits in doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (resulting in approximately 3 times and 2 times, respectively, the systemic exposure to minocycline observed in patients as a result of use of SOLODYN).

Reduced mean fetal body weight was observed in studies in which minocycline was administered to pregnant rats at a dose of 10 mg/kg/day (which resulted in approximately the same level of systemic exposure to minocycline as that observed in patients who use SOLODYN).

Minocycline was assessed for effects on peri-and post-natal development of rats in a study that involved oral administration to pregnant rats from day 6 of gestation through the period of lactation (postpartum day 20), at dosages of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (resulting in approximately 2.5 times the systemic exposure to minocycline observed in patients as a result of use of SOLODYN). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

Impairment of Fertility: Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (which resulted in up to approximately 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN) adversely affected spermatogenesis. Effects observed at 300 mg/kg/day included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

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Limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis.

SOLODYN should not be used by individuals of either gender who are attempting to conceive a child.

5.5.5. Other Toxicology Studies

Study 1 Buehler Sensitization Test of FMX-101 in Guinea Pigs (Study # S14544, GLP)

The potential of minocycline foam to produce sensitization after repeated topical applications was evaluated in guinea pigs using Buehler Sensitization Test.

A total of 39 adult female guinea pigs were used with 11 animals in each of three test groups (minocycline foam, 4%, 8% and 16%), and 6 animals in a vehicle control group. Animals were topically administered designated dosing formulations in two test phases (induction and challenge). Each animal was dosed 3 times per week over three 3 consecutive weeks during the induction phase followed by 1 dose in the challenge phase 13 days post the last induction dose. Dose sites were occluded for approximately 6 hours for each dose application. Dermal scoring was performed at 24 and 48 hours post challenge dose patch removal.

Discrete erythema was observed in one animal in the low dose group and two animals in the high dose group at the 24-hour time point, which was considered to be caused by non-specific irritation to the test article or wrapping procedures after challenge phase dosing. No erythema and/or edema were observed in any animals from the vehicle control group or the mid dose group at the 24-hour time point or any dose group at the 48-hour time point after challenge phase dosing.

In conclusion, minocycline foam did not cause a sensitization reaction under the conditions of this assay.

Study 2 Bovine Corneal Opacity and Permeability Test of FMX- 101 4% Foam, Lot 6080801 (Study # MB 16-24499.09, GLP)

The potential of minocycline foam, 4% to cause ocular irritation was evaluated using the Organisation for Economic Cooperation and Development (OECD) Bovine Corneal Opacity and Permeability Test based on the methodology described in the current OECD Guideline for the Testing of Chemicals No. 437.

Three bovine corneas per group were dosed with 0.75 ml of Minimal Essential Media (negative control), or 100% ethanol (positive control). The test article and vehicle control were dosed by dispensing either minocycline foam, 4% or vehicle foam as a one-second-burst (one depression from the canister) onto the exposed corneal epithelium at a distance of 10 cm to ensure that the entire cornea was covered. Following a 10-minute exposure for each group of dosed corneas, opacity measurements and sodium fluorescein permeability were determined.

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Based on an In Vitro Irritancy Score of less than 3, no category can be assigned for the United Nations Globally Harmonized System categorization of minocycline foam, 4% as defined in OECD Guideline 1\10. 437. According to European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) Database on Alternative Methods to Animal Experimentation (DB-ALM) Protocol 127, minocycline foam, 4% was considered to be a non-irritant to the eye.

ZILXI (minocycline) topical foam, 1.5% has the identical formulation except that the concentration of minocycline is 2.7-fold lower with a compensatory increase in the amount of light mineral oil.

Study 3 Bovine Corneal Opacity and Permeability Test of Minocycline HCl Powder, Batch 05NY01.HQ01055 (Study # MB 16-24500.09, GLP)

The potential of minocycline HCl to cause ocular irritation was evaluated using OECD Bovine Corneal Opacity and Permeability Test based on the methodology described in the current OECD Guideline for the Testing of Chemicals No. 437.

Three bovine corneas per group were dosed with 0.75 ml of a 20% (200 mg/ml) formulation of minocycline HCl powder in 0.9% Sodium Chloride, Minimal Essential Media (negative control), or a 20% formulation of imidazole in 0.9% saline (positive control). Vehicle controls were dosed with 0.75 ml of 0.9% Sodium Chloride. Following a four-hour exposure for each group of dosed corneas, opacity measurements and sodium fluorescein permeability were determined.

Based on an In Vitro Irritancy Score between 3 and 55, no prediction can be made for the United Nations Globally Harmonized System categorization of the test article, as defined in OECD Guideline No. 437. According to EURL ECVAM DB-ALM Protocol 127, Minocycline HCl powder was considered to be a mild eye irritant.

Impurities

The Applicant provided a comparison of the impurity profiles for minocycline foam, 4% to that of the LD SOLODYN as a surrogate for the comparison of the impurity profiles for minocycline foam, 1.5% to that of the LD SOLODYN in this NDA. No impurities were observed in minocycline topical foam, 1.5% above the identification threshold of (b) (4)% except for (b) (4) based on the impurity data generated for minocycline foam, 1.5% using a validated analytical test method.

The Applicant proposed two specifications for drug product impurities/degradants for minocycline foam, 1.5%, (b) (4) which are the same as those for minocycline foam, 4%. The Applicant proposed a rationale for these two specifications based on the level of these two impurities in the minocycline foam used in the 39-week dermal toxicity study in minipigs. The Applicant's rationale is acceptable. There are no concerns with the qualification of these impurities at the proposed level from a Pharmacology/Toxicology perspective based on available nonclinical data submitted by the Applicant.

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Refer to the Nonclinical Pharmacology/Toxicology section of NDA 212379 Multi-Disciplinary Review and Evaluation for details.

6. Clinical Pharmacology

6.1. Executive Summary

Minocycline hydrochloride is a broad-spectrum bacteriostatic and anti-inflammatory agent. The Applicant developed minocycline foam, 1.5% as a topical once daily treatment of inflammatory lesions (b) (4) of rosacea (b) (4) in subjects ≥18 years of age. To support the NDA submission, the Applicant conducted 2 clinical pharmacology studies: A maximal use PK study in adult subjects with PPR and a relative BA study in subjects with acne vulgaris with SOLODYN tablets as a LD). Under maximal use conditions, plasma minocycline concentrations following topical application of minocycline foam, 1.5% in subjects with PPR are expected to be lower than the LD, thus supporting establishment of a clinical bridge with SOLODYN tablets.

6.1.1. Recommendations

From clinical pharmacology perspective, the overall data provided in this NDA supports the approval of the drug product for the treatment of inflammatory lesions (b) (4) of rosacea in adults.

6.1.2. Postmarketing Requirement/Postmarking Commitment

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The relative BA study (#FX2014-03) using SOLODYN as a LD and minocycline foam, 4% formulation demonstrated that the mean ± standard deviation (SD) plasma minocycline maximum concentration (C_{max}) following topical application of minocycline foam, 4% (FMX101) was 1.7±0.8 ng/mL compared to 873.4±220 ng/mL with oral SOLODYN and the AUC were 31.8±15.0 h.ng/mL and 15227.3±3624.3 h.ng/mL following topical and oral administrations, respectively. There was no apparent accumulation observed following repeated topical once daily (QD) of minocycline foam, 4% to subjects with acne for 21 days (Figure 2). Relative BA of minocycline for FMX101 on Days 12 and 21 as compared to SOLODYN tablets was 0.126% and 0.131%, respectively, based on Cmax, and was 0.134% and 0.137%, respectively, based on AUC (Table 4).

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For additional information on relative BA study between FMX101 4% foam and SOLODYN tablets, refer to Section 6 and Section 19.4 in the Unireview dated 10/18/2019 under NDA 212379.

The Applicant conducted the relative BA study using FMX101 containing 4% minocycline instead of 1.5% which is the strength in the final to-be-marketed formulation (FMX103) in this application for the treatment of PPR. It should be noted that FMX101 formulation contains higher strength (4%) of minocycline HCl than FMX103 (1.5%). Furthermore, FMX101 4% for the treatment of acne vulgaris was approved on 10/18/2019 under NDA 212379.

Since the dosage form of FMX101 and FMX103 is the same, the Applicant has used data from the clinical bridge constructed under NDA 212379 to support the development of a lower strength formulation of FMX103 (1.5%) under 505(b)(2) regulatory pathway without conducting any relative BA study between FMX103 and the LD SOLODYN tablets. This indirect approach and cross study comparison to support 505(b)(2) regulatory pathway for FMX103 (1.5% foam) is reasonable due to very large difference in the systemic exposure observed in the relative BA study between FMX101 (4% foam) and SOLODYN tablets which supported approval of NDA 212379. Based on this, a similar large magnitude of difference in systemic exposure is expected between FMX103 (1.5% foam) and SOLODYN tablets and a relative BA study to support establishment of a clinical bridge was deemed not necessary. It should be noted that the Applicant of NDA 212379 and the Applicant of this NDA submission is the same.

In conclusion, under maximal use conditions, the plasma minocycline concentrations following topical application minocycline foam, 1.5% in patients with PPR are expected to be lower than the LD, thus supporting establishment of a clinical bridge with LD (SOLODYN tablets).

The clinical pharmacology study in this NDA consists of a maximal use PK study (#FX2017-14) using the final to-be-marketed formulation of FMX103 in subjects with PPR. Subjects received topical QD application of approximately 2 g of FMX103 to the full face for 14 days. Mean ± SD C_{max} of plasma minocycline on Days 1 and 14 were 1.3±0.9 ng/mL and 0.7±0.5 ng/mL, respectively Table 5. Mean ± SD $AUC_{0\text{-}tau}$ of plasma minocycline on Days 1 and 14 were 22.5±16.2 ng·h/mL and 15.8±11.4 ng·h /mL, respectively Table 5.

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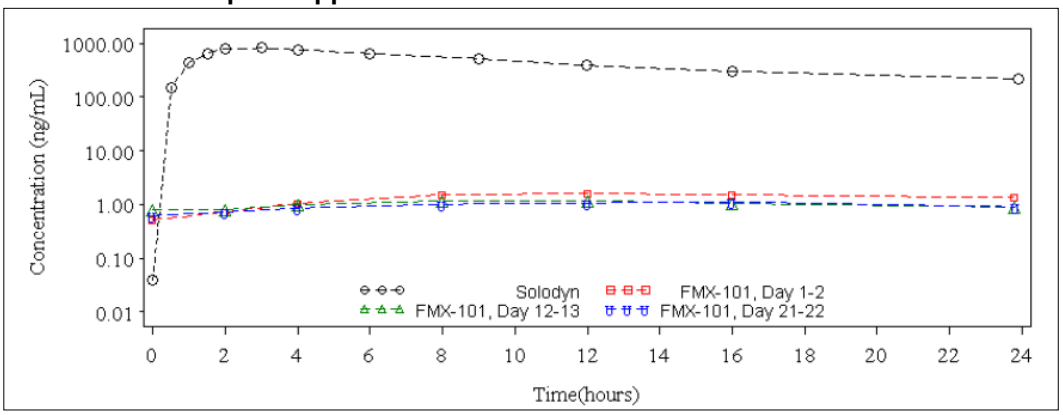
Figure 2: Mean Plasma Minocycline Concentration-Time Profile Following Oral Administration of SOLODYN and Topical Application of FMX101 4% in Acne Patients



Source: Figure 6 in 2.7.2 Summary of Clinical Pharmacology studies

Table 4: Summary of Bioavailability Analysis Following Single Dose Oral Administration of SOLODYN and Multiple Topical Application of FMX101 4% for 21 Days to Acne Patients

FMX101 4% vs. Solodyn	N	Log-Scale Difference of LSM [1]		Geometric LSM Ratio (%) (GMR) [2]	
		Estimate	90% CI	Estimate	90% CI
Day 12 C_{max}	29	-6.68	-6.91, -6.45	0.126	0.100, 0.159
Day 21 C_{max}	30	-6.64	-6.78, -6.50	0.131	0.113, 0.151
Day 12 AUC [3]	29	-6.62	-6.81, -6.42	0.134	0.110, 0.163
Day 21 AUC [4]	30	-6.59	-6.72, -6.46	0.137	0.121, 0.156

1. PK parameters from Reference (Period 1 (Day 1-5), Solodyn), Test Day 12 of Period 2 (FMX101), and Test Day 21 of Period 2 (FMX101 4%) are included in the analysis. Natural log-transformed quantities are analyzed in a mixed effects analysis of variance model, with treatment as a fixed effect and subject as a random effect.
Subjects must have results for PK parameters in both periods to be included in each assessment.
2. Geometric LSM ratio (GMR) and the associated 90% CI are back transformed point estimate and the associated 90% CI.
3. Day 12 $AUC_{0\text{-}tau}$ for FMX101 4% compared to $AUC_{0\text{-}inf}$ for Solodyn.
4. Day 21 $AUC_{0\text{-}tau}$ for FMX101 4% compared to $AUC_{0\text{-}inf}$ for Solodyn.
LSM=least squares mean; GMR =geometric mean ratio; CI = confidence interval.

Source: Table 12 in 2.7.2 Summary of Clinical Pharmacology studies

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Table 5: Summary of PK Parameters of Minocycline in Subjects With Papulopustular Rosacea Treated With FMX103 1.5%

		All Subjects (N=19)	
PK Parameter	**Statistic**	**Day 1**	**Day 14**
C_{max} (ng/mL)	n	19	19
	Mean (SD)	1.30 (0.916)	0.745 (0.543)
	CV (%)	70.3	72.8
	Geometric Mean[1]	1.05	0.614
	Median	0.915	0.526
	Minimum, Maximum	0.346, 3.41	0.285, 2.04
T_{max} (h)	n	19	19
	Mean (SD)	11.8 (4.07)	9.5 (3.82)
	CV (%)	34.5	40.3
	Median	12.0	8.0
	Minimum, Maximum	8, 24	4, 16
$AUC_{0\text{-tldc}}$ (ng*h/mL)	n	19	19
	Mean (SD)	21.3 (16.2)	23.1 (34.1)
	CV (%)	76.1	147.3
	Geometric Mean[1]	16.2	11.2
	Median	14.8	9.93
	Minimum, Maximum	3.26, 59.3	0.285, 142
C_{24} (ng/mL)	n	18	16
	Mean (SD)	0.863 (0.643)	0.566 (0.424)
	CV (%)	74.5	74.8
	Geometric Mean[1]	0.709	0.476
	Median	0.639	0.388
	Minimum, Maximum	0.298, 2.68	0.276, 1.68
$AUC_{0\text{-tau}}$ (ng*h/mL)	n	18	16
	Mean (SD)	22.5 (16.2)	15.8 (11.4)
	CV (%)	72.0	72.0
	Geometric Mean[1]	17.9	13.2
	Median	15.3	10.8
	Minimum, Maximum	7.36, 59.9	6.95, 43.6
R_{ACC}	n	NA	15
	Mean (SD)	NA	0.772 (0.342)
	CV (%)	NA	44.3
	Geometric Mean[1]	NA	0.684
	Median	NA	0.773
	Minimum, Maximum	NA	0.258, 1.28

$AUC_{0\text{-tau}}$ = area under the concentration-time curve from time zero (predose) through 24 hours; $AUC_{0\text{-tldc}}$ = area under the concentration-time curve from time zero (predose) to the time of last determinable concentration; C_{24} = plasma minocycline concentration 24 hours after FMX103 1.5% application; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; NA = not applicable; PK = pharmacokinetic; R_{ACC} = accumulation ratio; T_{max} = time to maximum measured plasma concentration

[1] Analysis was performed on log-transformed values. Geometric mean was converted to the original scale by calculating the anti-log

Source: Table 8 in 2.7.2 Summary of Clinical Pharmacology studies

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposed a dosing regimen of a small amount of topical minocycline foam, 1.5% (e.g., a cherry-sized amount) to be applied as a thin layer over all areas of the face once daily. If necessary, additional foam may be used to ensure the entire face is treated. The minocycline foam, 1.5% should be applied at approximately the same time each day at least 1 hour before

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bedtime. The Applicant's proposed dosing regimen appears consistent with the dosing regimens used in Phase 3 trials. Thus, the efficacy and safety results in Phase 3 trials support the proposed dosing regimen. For efficacy and safety findings, refer to clinical and statistical reviews in Sections 7 and 8.

Therapeutic Individualization

Therapeutic individualization is not applicable. No studies were conducted for assessment of the effects of intrinsic and extrinsic factors on the PK of the minocycline foam, 1.5% and this is not deemed necessary as the Applicant has followed a 505(b)(2) regulatory pathway and the systemic exposure of the minocycline foam, 1.5% is expected to be lower than that of the oral LD.

Outstanding Issues

There are no outstanding issues that would preclude the approval of minocycline foam, 1.5% from the clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology properties and PK characteristics of minocycline foam, 1.5% are summarized in Table 6.

Table 6: Summary of Pharmacology and PK Profile of Minocycline Foam, 1.5%

Pharmacology	
Mechanism of action	The mechanism of action and the pharmacodynamics of minocycline for the treatment of PPR is unknown.
Pharmacokinetics	
Adults under maximal use condition (Study FX2017-14)	Adult male and female subjects (N=20) with PPR received topical QD application of approximately 2 gm of minocycline foam, 1.5% to the entire face for 14 days. Mean ± SD C_{max} of plasma minocycline on Days 1 and 14 were 1.3±0.9 ng/mL and 0.7±0.5 ng/mL, respectively. Mean ± SD $AUC_{0\text{-}tau}$ of plasma minocycline on Days 1 and 14 were 22.5±16.2 ng·h/mL and 15.8±11.4 ng·h /mL, respectively. The decrease in systemic exposure on Day 14 could have been due to resolution of the disease.
Adults under maximal use condition (Study FX2014-03)	Adult male and female subjects with acne vulgaris (N=30) applied approximately 4 gm of minocycline foam, 4% topically to the face, neck, upper chest, upper back, shoulder, and upper arms once daily for 21 days. Median T_{max} on Day 21 was 14 h (range: 4 to 24 h). The mean ± SD C_{max} and $AUC_{0\text{-}24h}$ were 1.3±0.6 ng/mL and 23.0±10.8 ng·h/mL, respectively, which accounted for 0.131% and 0.137% of C_{max} and AUC_{inf} following single oral dose of SOLODYN tablets (~1 mg/kg minocycline), respectively.

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Pharmacology	
General information	
Safety/tolerability under maximal use condition	There were no systemic safety concerns observed. In Study FX2014-03, daily application of 4 gm of minocycline foam, 4% for 21 days was safe and well-tolerated in adults, and no treatment-emergent-AEs were reported. In Study FX2017-14, daily application of 2 gm of minocycline foam, 1.5% for 14 days was safe and well-tolerated in adults, and no treatment-emergent-AEs were reported.
Bioanalysis	Validated LC-MS/MS methods were used to determine the concentration of minocycline in plasma samples. The results of bioanalysis validation and incurred sample reanalysis are acceptable. Sample storage time was within the established long-term stability range (See Section 14.4.2)

Abbreviations: LC-MS/MS = liquid chromatography with tandem mass spectrometry; AE = adverse events; PPR = papules and pustules of rosacea; QD = once daily; AUC = area under the concentration time curve; SD = standard deviation

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of minocycline foam, 1.5% was not assessed in the maximal use PK study FX2017-14, rather this study supports systemic safety of the product. The data from Phase 3 trials support the effectiveness of the minocycline foam, 1.5% (See Sections 7 and 8 for details).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed topical QD application to facial lesions is acceptable for the treatment of (b) (4). Under maximal use conditions (i.e. approximately 2 gm topical QD application to the entire face), the systemic exposure of minocycline foam, 1.5% is expected to be lower than oral minocycline tablets (SOLODYN).

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Alternative dosing regimen for subpopulation, for example pediatric population, is not necessary as the proposed target population is adult subject 18 years and older (b) (4).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Given the topical product, food-drug interaction is not applicable in this scenario. The drug-drug interaction studies were not conducted because the Applicant followed a 505(b)(2) regulatory pathway and the systemic exposure of proposed topical product is expected to be markedly lower than the oral LD.

Reference ID: 4616286

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7: Listing of Clinical Trials Relevant to NDA 213690

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
FX2016-11	Multicenter, double-blind, vehicle controlled, randomized (2:1 active: vehicle)	Minocycline foam 1.5% or vehicle control applied topically once-daily	Coprimary efficacy: absolute change from baseline in the inflammatory lesion count at Week 12; AND IGA Treatment Success (dichotomized as yes/no) at Week 12, where success was defined as an IGA score of 0 or 1, and at least a 2-grade improvement (decrease) from baseline.	12 weeks	751	Male and female subjects 18 years of age and older with 15-75 facial papules and pustules, ≤2 nodules, IGA score 3 or 4, hx erythema or flushing of face	54 sites, all in U.S.
FX2016-12	Multicenter, double-blind, vehicle controlled, randomized (2:1 active: vehicle)	Minocycline foam 1.5% or vehicle control applied topically once-daily	Same as FX2016-11	12 weeks	771	Same as FX2016-11	46 sites, all in U.S.

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Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
FX2016-13	Multicenter, open-label (long-term extension to FX2016-11 and FX2016-12)	Minocycline foam 1.5% applied once-daily as necessary	Coprimary efficacy: absolute change from baseline in the inflammatory lesion count at Week 40; AND dichotomized IGA Treatment Success at Week 40	40 weeks	505	Same as FX2016-11 and FX2016-12	70 sites, all in U.S.
FX2015-10	Multicenter, double-blind, vehicle-controlled, dose ranging, randomized (1:1:1)	Minocycline foam 1.5%, Minocycline foam 3% and vehicle applied topically once-daily	Absolute change from baseline in the inflammatory lesion count at Week 12	12 weeks	233	Male and female subjects 18 years of age and older with moderate to severe rosacea by IGA and ≥12 facial papules and pustules	18 sites, all in Germany
FX2017-04	Single-center, nonrandomized, open-label, single-period, PK and safety study under conditions of maximal use	Approximately 2 grams Minocycline foam 1.5% applied topically once-daily to the full face	PK of minocycline after multiple doses of Minocycline foam, 1.5%	14 days	20	Adult subjects with moderate-to-severe facial papulopustular rosacea defined as IGA score 3 or 4	U.S.:1
FX2014-03	Single-center, nonrandomized, open-label, active-controlled 2-period, 2-treatment crossover bridging PK study at maximal use conditions	Two periods: single oral dose SOLODYN (~1 mg/kg); washout; Minocycline foam 4% ~4 g QD for 21 days	PK of minocycline after multiple doses of Minocycline foam 4%; relative bioavailability of Minocycline foam 4% foam compared to SOLODYN (minocycline HCl) extended release tablets	Minocycline foam 4%: 21 days	30	Adults with acne vulgaris and IGA score 3 (“moderate”)	U.S.: 1

Reference ID: 4616276

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
FX2016-06	Single-center, controlled, randomized, within-subject comparison study to evaluate the phototoxicity potential in healthy adult volunteers – dermal safety study	Minocycline foam 4% and vehicle foam under occlusive patch conditions and irradiated at 3- and 24-hours post-dose	Comparison with controls of the phototoxic response to Minocycline foam 4%	Single application with follow up at 21, 45, 69, and 93 hours	32	Healthy adults	U.S.: 1
FX2016-07	Randomized, single-center, controlled, evaluator-blinded, within-subject comparison study to evaluate the sensitizing potential in healthy adult volunteers – dermal safety study	Minocycline foam 4%, vehicle foam, and positive (SLS) and negative (saline) controls under occlusive patch conditions	Proportion of subjects with evidence of sensitization after repeated application under occlusion	Total of 10 patch applications over 6-8 weeks	233	Healthy adults	U.S.: 1

Reference ID: 4616276

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
FX2016-08	Randomized, single-center, controlled, evaluator-blinded, within-subject comparison study to evaluate the cumulative irritation potential in healthy adult volunteers – dermal safety study	Minocycline foam 4%, vehicle foam, and positive (SLS) and negative (saline) controls under occlusive patch conditions	Proportion of subjects with skin irritation after repeated application under occlusion	21 consecutive applications	42	Healthy adults	U.S.: 1
FX2016-09	Single-center, controlled, randomized, within-subject comparison study to evaluate the photoallergic skin reaction potential in healthy adult volunteers – dermal safety study	Minocycline foam 4% and vehicle foam under occlusive patch conditions and irradiated at 24 hours post-dose multiple times during induction and challenge phases	Comparison with controls of the photoallergic response to the investigational product	1 application	56	Healthy adults	U.S.: 1

Abbreviations: DB = double-blind; IGA = Investigator Global Assessment, No. = number; OL = open-label; PK = pharmacokinetic; QD = once daily; SLS = sodium lauryl sulfate.
Source: Applicant's Submission, Module 5.2, pp.1-5; also Clinical study reports for listed studies

Reference ID: 4616276

7.2. Review Strategy

Data Sources

The data sources used for the evaluation of the efficacy and safety of minocycline foam, 1.5% included the Applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format and was entirely electronic. Both Study Data Tabulation Model datasets and Analysis Data Model datasets were submitted. The analysis datasets used in this review are archived at: Application 213690 - Sequence 0003 - Data Analysis Data -

Data and Analysis Quality

The statistical and clinical teams evaluated the data fitness. In general, the data submitted by the Applicant to support the safety and efficacy of minocycline foam, 1.5% for the proposed indication appear adequate.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

8.1.1. Phase 3 Trials FX2016-11 and FX2016-12

8.1.1.1. Trial Design and Endpoints

The Applicant conducted two identically designed, randomized, multicenter, double-blind, vehicle-controlled, Phase 3 trials, Trial FX2016-11 and Trial FX2016-12, to evaluate the safety and efficacy of minocycline foam 1.5% for the treatment of inflammatory lesions (b) (4) of rosacea.

The following were the key inclusion criteria for the two trials:

- Male or female ≥18 years-of-age
- Moderate to severe rosacea per the IGA score (see Table 8) on the proposed facial treatment area consisting of:
  - At least 15 and not more than 75 facial papules and pustules, excluding lesions involving the eyes and scalp
  - No more than 2 nodules on the face
- Presence of or history of erythema and/or flushing on the face

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Table 8: Investigator Global Assessment (IGA) Scale for Trials FX2016-11/12

Score	Grade	Description
0	Clear	No inflammatory papules or pustules
1	Almost clear	Few inflammatory papules or pustules
2	Mild	Several inflammatory papules or pustules
3	Moderate	Moderate number of inflammatory papules or pustules and no nodules
4	Severe	Many inflammatory papules or pustules, and up to 2 nodules

Source: Applicant's Protocols FX2016-11/12

The protocols specified enrolling and randomizing approximately 750 subjects from approximately 40 centers in the USA in a 2:1 ratio to minocycline foam, 1.5% or vehicle foam, with randomization stratified by investigational center. Subjects were instructed to apply the study drug once daily for 12 weeks. Subjects had trial visits at Weeks 2, 4, 8, and 12, with efficacy assessments conducted at Weeks 4, 8, and 12. A safety follow-up call was to be conducted 4 weeks after the trial for those subjects who did not participate in the open-label Trial FX2016-13.

The severity of each of the following local signs and symptoms was measured at screening, baseline, and at each trial visit: erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation.

For both Phase 3 trials, the protocols specified the following coprimary efficacy endpoints:

- Absolute change from baseline in the inflammatory lesion count at Week 12
- IGA success at Week 12, defined as an IGA score of 0 (clear) or 1 (almost clear) and at least a 2-grade improvement (decrease) from baseline

The protocols specified the following secondary efficacy endpoints:

- Dichotomized IGA score, where success is defined as a 2-step improvement in score at Week 12 compared to baseline
- Percent change from baseline in the inflammatory lesion count at Week 12
- Absolute change from baseline in the inflammatory lesion count and IGA success at Week 8
- Absolute change from baseline in the inflammatory lesion count and IGA success at Week 4

The protocols also specified as tertiary efficacy endpoints the percent change from baseline in the inflammatory lesion count at Weeks 4 and 8; however, such endpoints were not included in the multiplicity testing strategy. Therefore, these endpoints are not presented in this review.

8.1.1.2. Statistical Methodologies

<u>Analysis Populations:</u>

The primary analysis population specified in the protocols and Statistical Analysis Plans (SAPs) was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocols/SAPs also specified supportive efficacy analyses for the coprimary endpoints using the per-protocol

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(PP) population, defined as "the subset of the ITT population without any protocol deviations that may have an impact on the efficacy assessments." Subjects to be included in the PP population were determined by the Applicant prior to unblinding of the trial. According to the SAPs, subjects with a protocol deviation whose severity is classified as 'Not Evaluable' were to be excluded from the PP population. Subjects were to be excluded from the PP population if any of the following were met:

- Failure to meet inclusion/exclusion criteria
- Have been administered any interfering concomitant medications
- Have not been compliant with the treatment regimen (e.g., less than 80% compliant)
- Did not complete Week 12 efficacy assessments
- Randomization error

Analysis methods for the coprimary endpoints:

The protocols/SAPs specified analyzing the coprimary endpoint of absolute change from baseline in inflammatory lesion count using analysis of covariance (ANCOVA) with treatment as a main effect, baseline value as a covariate, and analysis center as a blocking factor. The SAPs specified assessing homogeneity among analysis centers by including an analysis center-by-treatment interaction term in the ANCOVA model of the ITT observed cases (i.e., no imputation for missing data) analysis of the inflammatory lesion count endpoint. The SAPs stated that "analysis center by treatment interaction will be tested at the 0.1 level, and if significant, will further be explored." To account for the possibility of extreme outliers in the analysis of the inflammatory lesion count endpoint, the SAPs specified an additional sensitivity analysis using rank-transformed data.

The protocols/SAPs specified analyzing the coprimary endpoint of IGA success (IGA score of 0 or 1 and at least a 2-grade improvement from baseline) using the Cochran-Mantel-Haenszel (CMH) test, stratified by analysis center. For the IGA success, the protocols specified assessing investigational center-by-treatment interaction using the Breslow-Day test (2-sided 0.1 level). If significant, the protocols specified further exploration through the examination of descriptive statistics by individual investigational center. However, the Breslow-Day test was not specified in the SAPs.

Pooling centers algorithm:

According to the SAPs, if an investigational center has randomized at least 30 subjects and has at least 16 subjects assigned to the minocycline foam, 1.5% arm and at least 8 subjects assigned to the vehicle arm, then this center satisfies the criteria of an 'analysis center.' Otherwise, the center is considered as a small site and the following algorithm was specified in the SAPs to pool small centers:

1. Small centers are ordered by site number.
2. From the first center into the next site, the number of subjects randomized to each treatment arm and total are added together until the pooled centers meet the criteria of an 'analysis center.'

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3. If there is (are) small center(s) left, the left-over small center(s) is (are) added to the last 'analysis center.'

An unspecified number of small centers could be combined to meet the criteria of an 'analysis center' until the prespecified criteria are met.

Analysis methods for the secondary efficacy endpoints:

The protocols/SAPs specified analyzing secondary efficacy endpoints similarly to the appropriate coprimary efficacy endpoint. The protocols stated that secondary endpoints would be tested sequentially in the order listed in Section 8.1.1.1 at the 0.05 level of significance if the coprimary endpoints were significant; however, the SAPs and the clinical study reports (CSRs) state that no adjustments were made for multiple comparisons of endpoints.

Methods for handling the missing data:

The primary imputation method for the handling of missing data for the analyses of the coprimary and secondary endpoints specified in the protocols/SAPs is the MI. For this method, intermittent missing values were imputed separately for each treatment arm using the Markov Chain Monte Carlo method. Ten copies of the dataset with a monotonic missing pattern were generated. For each of the 10 monotonic missing pattern datasets, an additional 10 datasets were imputed to replace missing values at scheduled visits (Weeks 4, 8, and 12) for a total of 100 datasets. The multiple regression model for monotone data was fitted for the inflammatory lesion count as the dependent variable and outcomes at previous visits and treatment arm as independent variables. The logistic regression method for monotone data was used for imputation of IGA success. A prespecified seed number of (b) (4) for Trial FX2016-11 and (b) (4) for Trial FX2016-12 was used in all imputation procedures. The analysis results (ANCOVA analysis for inflammatory lesion count and CMH analysis for the IGA success) were combined using Rubin's formula. All supportive analyses using the PP population used the observed-cases approach, i.e., no imputation for missing data at any time point.

For the analyses of the coprimary efficacy endpoints, the protocols/SAPs also specified sensitivity analyses for the handling of missing data to assess the robustness of alternate imputation assumptions using the last observation carried forward (LOCF) and the baseline observation carried forward methods. For the LOCF method, the baseline values were not carried forward.

8.1.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial FX2016-11 enrolled and randomized a total of 751 subjects (495 subjects to minocycline foam, 1.5% and 256 subjects to vehicle). Trial FX2016-12 enrolled and randomized a total of 771 subjects (514 subjects to minocycline foam, 1.5% and 257 subjects to vehicle). Table 9 presents the disposition of subjects. The discontinuation rates were generally similar across the two trials. The most common reasons for discontinuation for both trials were 'lost to follow-up' and 'withdrawal by subject'.

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Table 9: Subject Disposition for Trials FX2016-11/12 (ITT*)

	Trial FX2016-11		Trial FX2016-12	
	Minocycline Foam, 1.5% N=495	**Vehicle Foam N=256**	**Minocycline Foam, 1.5% N=514**	**Vehicle Foam N=257**
Completed	437 (88%)	232 (91%)	479 (93%)	239 (93%)
Discontinued	58 (12%)	24 (9%)	35 (7%)	18 (7%)
Reasons of discontinuation				
Adverse event	5 (1%)	2 (1%)	2 (<1%)	0 (0%)
Lost to follow-up	25 (5%)	8 (3%)	15 (3%)	9 (4%)
Withdrawal by subject	24 (5%)	12 (5%)	11 (2%)	7 (3%)
Protocol deviation	3 (1%)	1 (<1%)	1 (<1%)	0 (0%)
Other	1 (<1%)	1 (<1%)	6 (1%)	2 (1%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
*Intent-to-Treat (ITT) population is defined as all randomized subjects

The demographics for the two trials are presented in Table 10. The demographics were generally balanced across the treatment arms within each trial; however, in Trial FX2016-12, a slightly higher proportion of females were randomized to minocycline foam, 1.5% compared to the vehicle arm. The demographics were similar across the two trials. The majority of the subjects were female (approximately 70%) and white (approximately 97%). The mean age was approximately 50 years old.

Table 10: Demographics for Trials FX2016-11/12 (ITT*)

	Trial FX2016-11		Trial FX2016-12	
Demographic	**Minocycline Foam, 1.5% N=495**	**Vehicle Foam N=256**	**Minocycline Foam, 1.5% N=514**	**Vehicle Foam N=257**
Age (years)				
Mean (SD)	48.9 (13.7)	49.7 (12.9)	50.8 (13.9)	50.9 (13.5)
Median	49	49	51	51
Range	18 – 82	22 – 86	18 – 85	18 – 82
18 – 40	142 (29%)	58 (23%)	123 (24%)	60 (23%)
41 – 64	289 (58%)	162 (63%)	299 (58%)	149 (58%)
≥65	64 (13%)	36 (14%)	92 (18%)	48 (19%)
Sex				
Male	140 (28%)	70 (27%)	149 (29%)	89 (35%)
Female	355 (72%)	186 (73%)	365 (71%)	168 (65%)
Race				
White	474 (96%)	241 (94%)	499 (97%)	250 (98%)
Black or African American	7 (1%)	4 (2%)	7 (1%)	1 (<1%)
American Indian or Alaska Native	3 (1%)	0 (0%)	0 (0%)	2 (1%)
Native Hawaiian or Other Pacific Islander	3 (1%)	3 (1%)	0 (0%)	1 (<1%)
Asian	6 (1%)	6 (2%)	5 (1%)	2 (1%)
More than one race	2 (<1%)	1 (<1%)	2 (<1%)	0 (0%)
Ethnicity				
Hispanic or Latino	165 (33%)	88 (34%)	166 (32%)	86 (33%)
Not Hispanic or Latino	328 (67%)	168 (66%)	348 (68%)	171 (67%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
*Intent-to-Treat (ITT) population is defined as all randomized subjects
Note: In Trial FX2016-11, one subject in the vehicle arm (Subject (b) (6)) did not have value for race and two subjects in the active arm (Subjects (b) (6)) did not have values for ethnicity. In Trial FX2016-12, one subject in the vehicle arm (Subject (b) (6)) and one subject in the active arm (Subject (b) (6)) did not have values for race.

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Table 11 presents the baseline disease characteristics for both trials. The baseline disease characteristics were generally balanced across the treatment arms. In general, more subjects with an IGA score of 3 (moderate) were enrolled in the two trials (approximately 86%).

Table 11: Baseline Disease Characteristics for Trials FX2016-11/12 (ITT*)

	Trial FX2016-11		Trial FX2016-12	
	Minocycline Foam, 1.5% N=495	**Vehicle Foam N=256**	**Minocycline Foam, 1.5% N=514**	**Vehicle Foam N=257**
IGA				
3 – Moderate	444 (90%)	222 (87%)	443 (86%)	213 (83%)
4 – Severe	51 (10%)	34 (13%)	71 (14%)	44 (17%)
Inflammatory Lesions				
Mean (SD)	28.5 (12.1)	29.0 (12.1)	30.0 (12.8)	30.2 (13.0)
Median	25	25	26	26
Range	5** – 74	15 – 75	15 – 75	15 – 75

*Intent-to-Treat (ITT) population is defined as all randomized subjects
**The minimum value of 5 lesions in the Minocycline foam arm was due to Subject (b) (6) being included in the ITT population in spite of not meeting Inclusion criterion #2a (at least 15 and not more than 75 facial lesions). This subject was discontinued at Visit 1.
Abbreviations: IGA = Investigator's Global Assessment; SD = standard deviation
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

8.1.1.4. Results for the Coprimary Endpoints

Table 12 presents the proportion of subjects with missing primary IGA assessments by treatment arm at each trial visit. Missing data was generally balanced across the treatment arms in each trial. However, Trial FX2016-11 has slightly more missing data compared to Trial FX2016-12. The amount of missing inflammatory lesion count assessments at each visit (not shown here) is the same as shown in Table 12.

Table 12: Missing IGA Assessments by Visit for Trials FX2016-11/12 (ITT)*

	Trial FX2016-11		Trial FX2016-12	
Week	**Minocycline Foam, 1.5% N=495**	**Vehicle Foam N=256**	**Minocycline Foam, 1.5% N=514**	**Vehicle Foam N=257**
Week 6	29 (6%)	12 (5%)	23 (4%)	11 (4%)
Week 8	45 (9%)	21 (8%)	39 (8%)	11 (4%)
Week 12	72 (15%)	31 (12%)	40 (8%)	22 (9%)

* Intent-to-treat (ITT) population is defined as all randomized subjects
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

Table 13 presents the results of the coprimary efficacy endpoints for both trials in the ITT population. The multiple imputation method was used to impute missing data. In both trials, minocycline foam, 1.5% was statistically superior to vehicle for both coprimary efficacy endpoints (p-values <0.0218). The treatment effect for inflammatory lesion count endpoint was slightly higher in Trial FX2016-12 compared to Trial FX2016-11. The results for the PP population (not presented here) were similar to those for the ITT population. The results of percent change from baseline in inflammatory lesion counts at Week 12 (i.e., a secondary efficacy endpoint) for both trials are supportive of the results for the absolute change, (see Table 15 in Section 8.1.1.6).

Reference ID: 4616286

As noted in Section 8.1.1.2, a sensitivity analysis of the inflammatory lesion count endpoint was conducted using rank-transformed data to account for the possibility of extreme outliers. The p-values from the ranked analyses of the absolute change from baseline in inflammatory lesion count at Week 12 were similar to the p-values from the unranked analyses in (see Table 8).

Table 13: Results of the Coprimary Endpoints at Week 12 for Trials FX2016-11/12 (ITT; MI*)

	Trial FX2016-11		Trial FX2016-12	
Endpoint	**Minocycline Foam N=495**	**Vehicle Foam N=256**	**Minocycline Foam, 1.5% N=514**	**Vehicle Foam N=257**
IGA success**	52.1%	43.0%	49.1%	39.0%
Treatment difference (95% CI) (1)	9.0% (1.3%, 16.8%)		10.2% (3.1%, 17.4%)	
P-value(1)	0.0218		0.0049	
Inflammatory lesions				
LS mean change from baseline (SE)	-17.6 (0.4)	-15.4 (0.6)	-18.4 (0.5)	-14.5 (0.7)
Treatment difference (95% CI) (2)	-2.2 (-3.7, -0.7)		-3.9 (-5.5, -2.2)	
P-value (unranked)(2)	0.0031		<0.001	
P-value (ranked)(2)	<0.001		<0.001	

* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
**IGA Success is defined as an IGA score of 0 or 1 and at least a 2-grade improvement from baseline
(1) Difference, 95% CI and p-value are based on the CMH test stratified by analysis center
(2) Difference, 95% CI and p-values are based on ANCOVA (ranked on unranked) model with treatment and analysis center as factors, and baseline value as covariate
Abbreviations: CI = Confidence Interval; LS means = least squares mean; SE = standard error
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

Table 14 presents the results of the coprimary endpoints across the various prespecified imputation methods described in Section 8.1.1.2. The results were generally similar across the various methods. It is noted that in Trial FX2016-11, the treatment effect for baseline observation carried forward is not significant (p-values >0.05) for the IGA success; however, it is in the same direction as the other methods of imputation.

As noted in Section 8.1.1.2, the Applicant excluded the subjects with only baseline value from the LOCF analysis. The statistical reviewer conducted LOCF analysis including all randomized subjects (i.e., without excluding subjects with only baseline value). The results for the statistical reviewer's LOCF analysis (see Table 14) were similar to the other methods, with treatment effects having the same direction; however, for Trial FX2016-11, the treatment effect in IGA success was not significant (p-value=0.0624).

Reference ID: 4616286

Table 14: Results of the Coprimary Endpoints at Week 12 With Different Approaches for Handling Missing Data for Trials FX2016-11/12 (ITT)*

	Trial FX2016-11		Trial FX2016-12	
ITT Population	**Minocycline Foam, 1.5% N=495**	**Vehicle Foam N=256**	**Minocycline Foam, 1.5% N=514**	**Vehicle Foam N=257**
IGA Success**				
Observed cases	53.0%	44.4%	49.6%	40.0%
Treatment effect	8.6%		9.6%	
P-value(3)	0.0344		0.0104	
LOCF – Applicant's analysis(1)	50.0%	41.8%	48.5%	38.6%
Treatment effect (95% CI)	8.2%		9.9%	
P-value(3)	0.0332		0.0062	
LOCF – Reviewer's analysis(2)	47.7%	40.6%	46.9%	37.4%
Treatment effect	7.1%		9.5%	
P-value(3)	**0.0624**		0.0071	
BOCF	45.3%	39.1%	45.7%	36.6%
Treatment effect	6.2%		9.1%	
P-value(3)	**0.0995**		0.0091	
Inflammatory Lesions – Change in LS means (SE)				
Observed cases	-17.9 (0.4)	-15.8 (0.6)	-18.6 (0.5)	-14.7 (0.7)
Treatment effect	-2.1		-3.9	
P-value(4)	0.006		<0.0001	
LOCF – Applicant's analysis(2)	-17.3 (0.5)	-14.8 (0.6)	-18.4 (0.5)	-14.4 (0.7)
Treatment effect	-2.5		-3.95	
P-value(4)	0.0013		<0.0001	
LOCF – Reviewer's analysis(2)	-16.5 (0.5)	-14.3 (0.6)	-17.7 (0.5)	-14.1 (0.7)
Treatment effect	-2.1		-3.5	
P-value(4)	0.0073		<0.0001	
BOCF	-15.3 (0.5)	-13.7 (0.7)	-17.1 (0.5)	-13.5 (0.7)
Treatment effect	-1.5		-3.6	
P-value(4)	**0.0644**		<0.0001	

* Intent-to-treat (ITT) population is defined as all randomized subjects
** IGA Success is defined as an IGA score of 0 or 1 and at least a 2-grade improvement (decrease) from baseline
Note: The treatment effect is the difference between minocycline foam, 1.5% and vehicle foam
(1) Applicant's LOCF analysis excludes subjects who only had baseline value
(2) Reviewer's LOCF analysis includes all randomized subjects
(3) P-Value obtained using the CMH test stratified by analysis center
(4) P-Value obtained for the difference in least square (LS) means using ANCOVA model with treatment and analysis center as factors, and baseline value as covariate
Abbreviations: BOCF = baseline-observation-carried-forward; LOCF = last-observation-carried-forward; IGA = Investigator Global Assessment
Source: Statistical Reviewer's Analysis

8.1.1.5. Efficacy Over Time

Subjects were evaluated for efficacy at Weeks 4, 8, and 12. Figure 3 presents the IGA success rates over time for Trials FX2016-11/12. Figure 4 presents the LS mean change from baseline in inflammatory lesion count over time for Trials FX2016-11/12. The efficacy results of minocycline foam, 1.5% and vehicle foam gradually separated over time through Week 12. The plots of efficacy over time appear similar across the two trials for both the coprimary efficacy endpoints.

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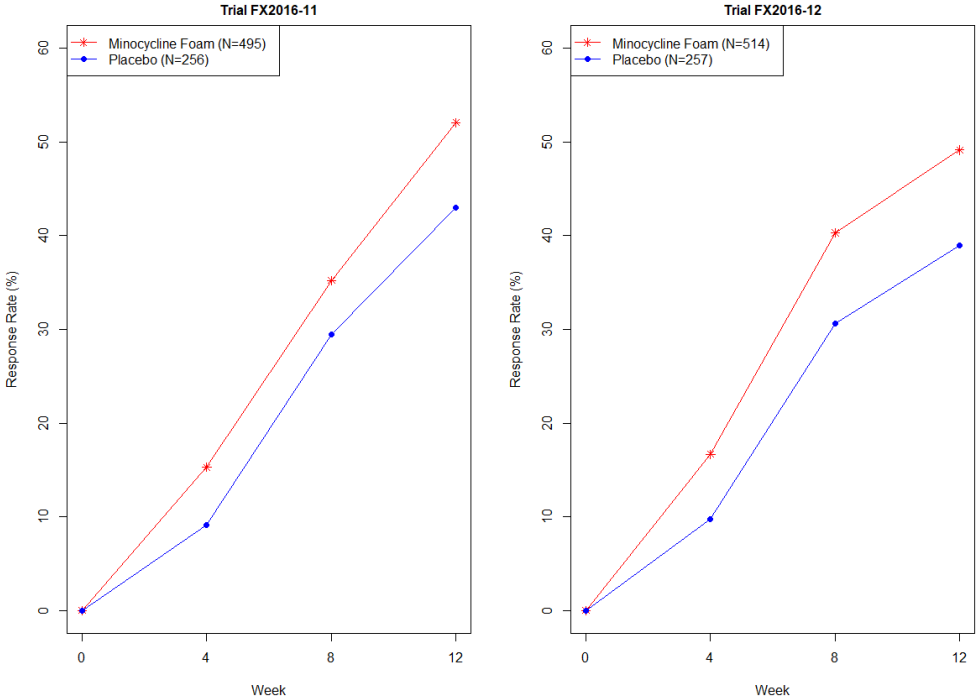
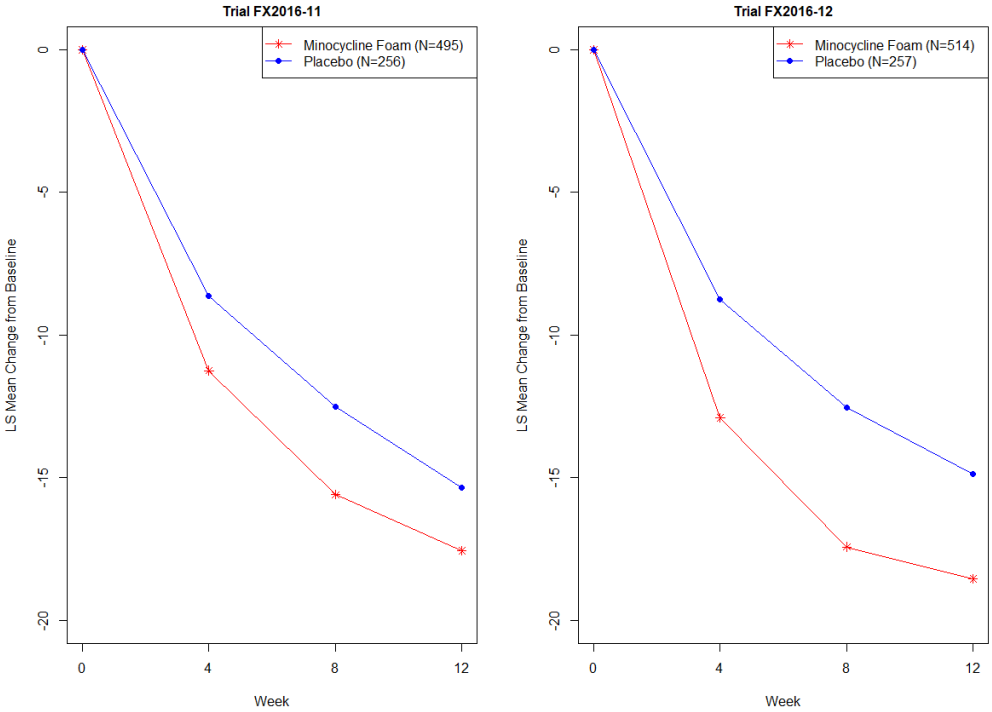
Figure 3: IGA Success Rates Over Time for Trials FX2016-11/12 (ITT; MI*)



*Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Source: Statistical Reviewer's Analysis

Figure 4: LS Mean Change in Inflammatory Lesion Counts Over Time for Trials FX2016-11/12 (ITT; MI*)



* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Source: Statistical Reviewer's Analysis

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8.1.1.6. Results for the Secondary Efficacy Endpoints

As noted in Section 8.1.1.2, the SAPs and CSRs state that no adjustments were made for multiple comparisons of endpoints. Therefore, the results of the secondary efficacy endpoints are viewed as exploratory for this review and p-values are not presented (see Table 15).

Table 15: Results of the Secondary Endpoints for Trials FX2016-11/12 (ITT; MI*)

	Trial FX2016-11		Trial FX2016-12	
	Minocycline Foam, 1.5% N=495	**Vehicle Foam N=256**	**Minocycline Foam, 1.5% N=514**	**Vehicle Foam N=257**
Week 12				
2-grade improvement on IGA	54.7%	44.8%	52.5%	43.8%
Treatment Effect (95% CI)	9.9% (2.0%, 17.8%)		9.7% (2.0%, 17.4%)	
Inflammatory Lesions – % Change				
LS Mean (SE)	-61.3% (1.6%)	-54.1% (2.1%)	-60.2% (1.6%)	-48.9% (2.3%)
Treatment Effect (95% CI)	-7.3% (-12.5%, -2.1%)		-11.3% (-16.7%, -5.9%)	
Week 8				
IGA Success	35.2%	29.4%	40.3%	30.7%
Treatment Effect (95% CI)	5.8% (-1.4%, 13.0%)		9.6% (2.4%, 16.9%)	
Inflammatory Lesions – Abs. Change				
LS Mean (SE)	-15.6 (0.4)	-12.5 (0.6)	-17.1 (0.5)	-12.1 (0.6)
Treatment Effect (95% CI)	-3.1 (-4.6, -1.6)		-5.1 (-6.6, -3.5)	
Week 4				
IGA Success	15.3%	9.1%	16.7%	9.7%
Treatment Effect (95% CI)	6.2% (1.3%, 11.0%)		6.9% (2.0%, 11.9%)	
Inflammatory Lesions – Abs. Change				
LS Mean (SE)	-11.2 (0.4)	-8.6 (0.6)	-12.7 (0.5)	-8.3 (0.7)
Treatment Effect (95% CI)	-2.6 (-4.1, -1.2)		-4.4 (-6.0, -2.8)	

* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Abbreviations: Abs. = absolute; ITT = intent-to-treat; MI = multiple imputation
Source: Statistical Reviewer's Analysis (same as Applicant's analysis)

8.1.1.7. Lesion Counts and IGA

We note that the IGA scale is described in terms of lesion counts only. Therefore, the statistical reviewer explored the range of lesion count for each of the IGA category/score. Table 16 and Table 17 present the mean, median, and range of lesion counts for each of the IGA score at baseline and Week 12, respectively, using the observed data. The same information is displayed in the boxplots in Figure 5 for baseline and Figure 6 for Week 12 (Trials FX2016-11 and FX2016-12, respectively).

In Trial FX2016-11, a total of 258 subjects had lesion counts between 30 and 75, inclusive, at baseline; 199 of these subjects (75%) were scored with IGA score of 3, and 65 subjects (25%) were scored with IGA score of 4. Similarly, in Trial FX2016-12, a total of 258 subjects had lesion counts between 34 and 75, inclusive, at baseline; 139 of these subjects (61%) were scored with IGA score of 3, and 88 subjects (39%) were scored with IGA score of 4. No clear-cut distinction in lesion count between IGA scores 3 and 4 and IGA scores 2 and 3 is seen in the results for Week 12 (see boxplots in Figure 6 and Figure 7). The observed inter-rater variability may be explained by either the investigators taking more aspects into account when assigning an IGA

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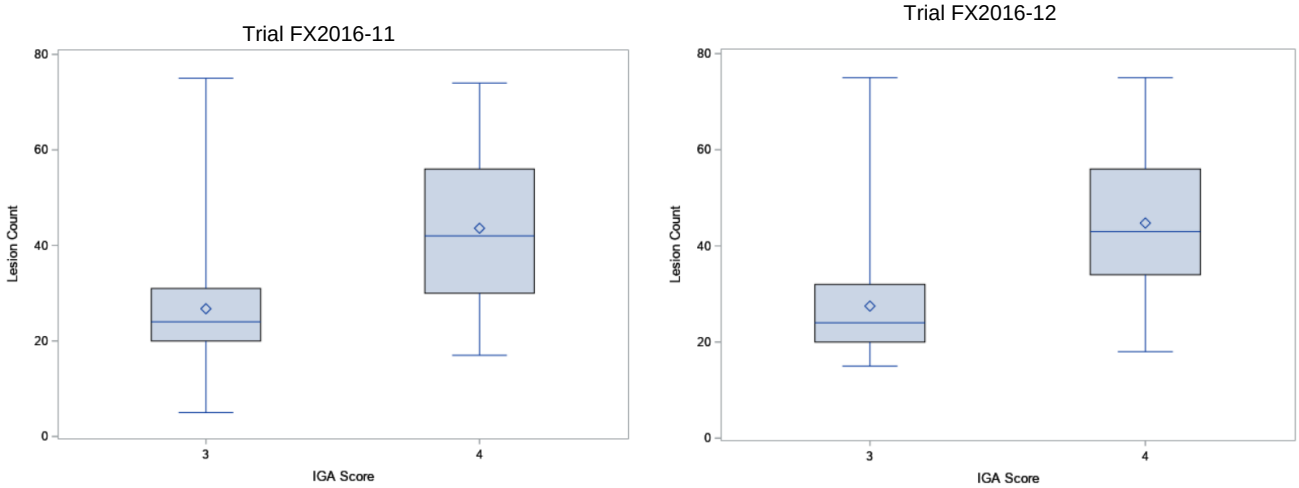
score besides the lesion count or by the different investigators translating “few”, “several”, “moderate number” and “many” lesions in different ways.

Table 16: Lesion Counts by IGA Score at Baseline (Observed Data) – Trials FX2016-11/12

	Trial FX2016-11				Trial FX2016-12			
	Lesion Count				Lesion Count			
IGA Score	N	Mean (SE)	Median	Range	N	Mean (SE)	Median	Range
Moderate – 3	666	26.7 (0.39)	24	5 – 75	656	27.5 (0.42)	24	15 – 75
Severe – 4	85	43.6 (1.72)	42	17 – 74	115	44.8 (1.33)	43	18 – 75

Source: Statistical Reviewer’s Analysis using observed data

Figure 5: Boxplots for Lesion Count by IGA Score at Baseline – Trials FX2016-11/12



Source: Statistical Reviewer’s Analysis using observed data

Table 17: Lesion Counts by IGA Score at Week 12 (Observed Data) – Trials FX2016-11/12

	Trial FX2016-11				Trial FX2016-12			
	Lesion Count				Lesion Count			
IGA Score	N	Mean (SE)	Median	Range	N	Mean (SE)	Median	Range
0 – Clear	56	0.5 (0.14)	0	0 – 4	54	0.30 (0.14)	0	0 – 6
1 – Almost Clear	268	4.7 (0.20)	4	0 – 19	275	5.6 (0.20)	5	0 – 18
2 – Mild	178	12.0 (0.5)	10.5	1 – 41	218	12.0 (0.41)	11	2 – 46
3 – Moderate	139	24.4 (0.83)	22	6 – 64	144	25.4 (1.07)	22.5	4 – 75
4 – Severe	7	44.7 (6.95)	44	19 – 72	18	53.1 (5.40)	50	25 – 113

Source: Statistical Reviewer’s Analysis using observed data

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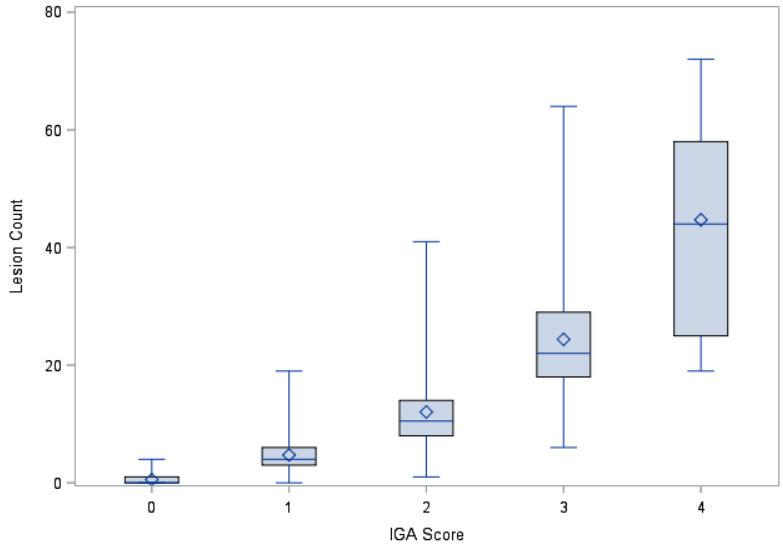
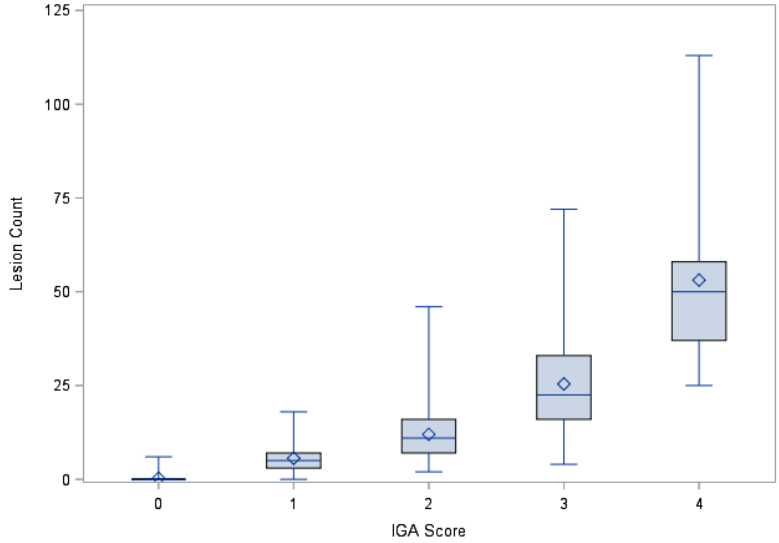
Figure 6: Boxplots for Lesion Count by IGA Score at Week 12 – Trial FX2016-11



Source: Statistical Reviewer's Analysis using observed data

Figure 7: Boxplots for Lesion Count by IGA Score at Week 12 – Trial FX2016-12



Source: Statistical Reviewer's Analysis using observed data

8.1.1.8. Findings in Special/Subgroup Populations

Sex, Race, Age, and Baseline Disease Severity

The results for the IGA success (i.e., IGA score of 0 or 1 with at least 2-grade of improvement from baseline) at Week 12 by age (<65 vs. ≥65), sex, race (white vs. non-white), and baseline IGA score (moderate vs. severe) for Trials FX2016-11 and FX2016-2 are presented in Figure 8 and Figure 9, respectively. However, we can't draw meaningful conclusions for the subgroup analyses by race and baseline IGA score due to the small number of subjects in the subgroups

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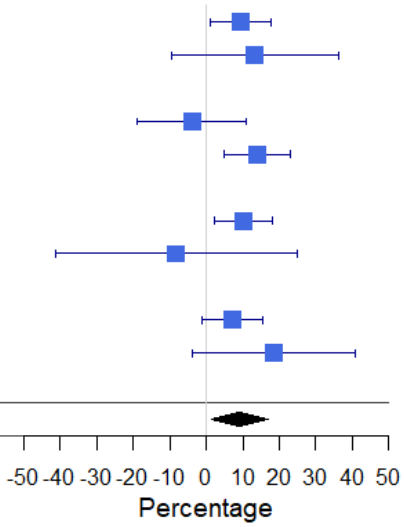
of non-white and severe baseline IGA score in both trials. The results for the absolute change in inflammatory lesion count at Week 12 by the same subgroups for Trials FX2016-11 and FX2016-2 are presented in Figure 10 and Figure 11, respectively. The forest plots in these figures contain 95% confidence intervals for the treatment effect between the active and vehicle arms for the ITT population using the MI method for the handling of missing data.

In Trial FX2016-11, a larger IGA success rate is observed for male subjects in the vehicle arm compared to male subjects in the minocycline arm; however, this effect was not observed in Trial FX2016-12. A similar effect is observed in IGA success rates for non-white subjects in Trial FX2016-11; however, the sample size for non-white is small to allow meaningful conclusions.

In both trials, the results for the absolute change in inflammatory lesion counts at Week 12 appear consistent across the subgroups presented in Figure 10 and Figure 11, with the exception of the non-white subgroup. In addition, a higher treatment effect is observed for the subgroup of subjects who had baseline IGA score of 4 (severe) for both coprimary endpoints in both trials. However, we can't draw meaningful conclusions for the subgroup analyses by race and baseline IGA score due to the small number of subjects in the subgroups of non-white and severe baseline IGA score in both trials.

Figure 8: IGA Success* at Week 12 by Age, Sex, Race, and Baseline IGA for Trial FX2016-11 (ITT; MI)**

Subgroups (n[FMX], n[V])	FMX103 (N=495)	Vehicle (N=256)	Difference
Age			
<65 (431, 220)	51.2%	42.1%	9.4%
>=65 (64, 36)	57.7%	48.7%	13.3%
Sex			
Male (140, 70)	45.8%	48.8%	-3.9%
Female (365, 186)	54.5%	40.8%	13.8%
Race			
White (474, 241)	52.0%	41.8%	10.2%
Non-White (21, 15)	53.9%	62.2%	-8.3%
Baseline IGA			
Moderate (444, 222)	53.9%	47.1%	7.1%
Severe (51, 34)	36.3%	16.3%	18.4%
Overall	**52.1%**	**43.0%**	**9.0%**



*IGA Success is defined as an IGA score of 0 or 1 and at least a 2-grade improvement from baseline
** Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Note: Difference and 95% CI and p-value are based on the CMH test stratified by analysis center. Stratification by analysis center was not performed for the small subgroups of non-white and baseline IGA of 4, where adjustment by analysis center caused zero frequencies
Abbreviations: FMX103: Minocycline Foam, 1.5%; CI: Confidence Interval; n[FMX] = subgroup sample size for active arm, n[V] = subgroup sample size for vehicle arm
Source: Statistical Reviewer's Analysis

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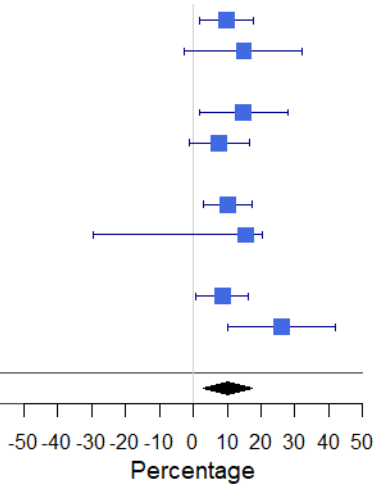
Figure 9: IGA Success* at Week 12 by Age, Sex, Race, and Baseline IGA for Trial FX2016-12 (ITT; MI)**

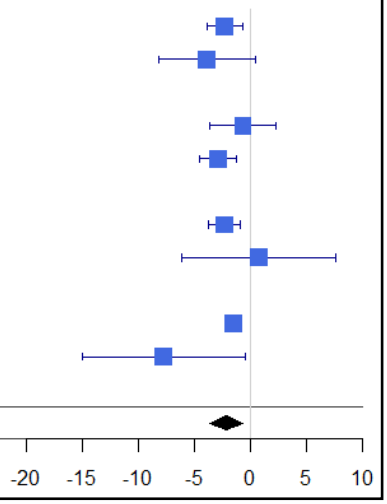
Subgroups (n[FMX], n[V])	FMX103 (N=514)	Vehicle (N=257)	Difference
Age			
<65 (422, 209)	47.7%	37.6%	9.8%
>=65 (92, 48)	55.5%	45.1%	14.9%
Sex			
Male (149, 89)	51.9%	39.1%	14.8%
Female (365, 168)	48.0%	38.9%	7.7%
Race			
White (499, 250)	49.2%	39.2%	10.2%
Non-White (15, 7)	47.5%	32.1%	15.4%
Baseline IGA			
Moderate (443, 213)	51.0%	44.2%	8.6%
Severe (71, 44)	37.1%	13.9%	26.0%
Overall	**49.1%**	**39.0%**	**10.2%**



*IGA Success is defined as an IGA score of 0 or 1 and at least a 2-grade improvement from baseline
** Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Note: Difference and 95% CI and p-value are based on the CMH test stratified by analysis center. Stratification by analysis center was not performed for the small subgroup of non-white, where adjustment by analysis center caused zero frequencies
Abbreviations: FMX103: Minocycline Foam, 1.5%; CI: Confidence Interval; n[FMX] = subgroup sample size for active arm, n[V] = subgroup sample size for vehicle arm
Source: Statistical Reviewer's Analysis

Figure 10: Absolute Change in inflammatory Lesion Counts at Week 12 by Age, Sex, Race, and Baseline IGA for Trial FX2016-11 (ITT; MI*)

Subgroups (n[FMX], n[V])	FMX103 (N=495)	Vehicle (N=256)	Difference in LS Means
Age			
<65 (431, 220)	-17.6	-15.8	-2.3
>=65 (64, 36)	-17.6	-13.7	-3.9
Sex			
Male (140, 70)	-18.2	-17.4	-0.7
Female (365, 186)	-17.3	-14.4	-2.9
Race			
White (474, 241)	-17.5	-15.2	-2.4
Non-White (21, 15)	-14.6	-15.3	0.7
Baseline IGA			
Moderate (444, 222)	-16.5	-14.9	-1.6
Severe (51, 34)	-24.3	-16.5	-7.8
Overall	**-17.6**	**-15.4**	**-2.2**



* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Note: LS Means are presented in this plot. Difference and 95% CI based on ANCOVA model with treatment and analysis center as factors, and baseline value as covariate.
Abbreviations: FMX103: Minocycline Foam, 1.5%; CI: Confidence Interval; n[FMX] = subgroup sample size for active arm, n[V] = subgroup sample size for vehicle arm
Source: Statistical Reviewer's Analysis

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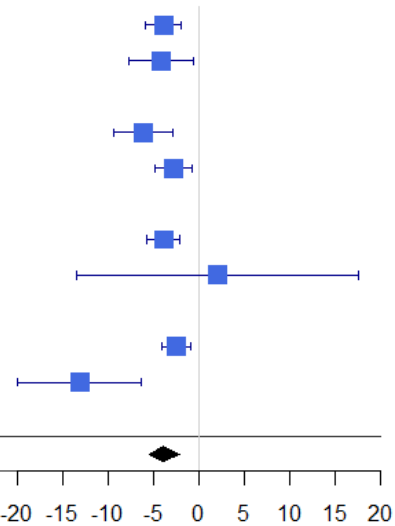
Figure 11: Absolute Change in inflammatory Lesion Counts at Week 12 by Age, Sex, Race, and Baseline IGA for Trial FX2016-12 (ITT; MI*)

Subgroups (n[FMX], n[V])	FMX103 (N=514)	Vehicle (N=256)	Difference in LS Means
Age			
<65 (422, 209)	-18.3	-14.4	-3.9
>=65 (92, 48)	-19.6	-15.4	-4.2%
Sex			
Male (144, 89)	-19.9	-13.7	-6.1%
Female (365, 168)	-17.6	-14.9	-2.8
Race			
White (474, 241)	-18.3	-14.4	-3.9
Non-White (21, 15)	-18.2	-20.3	2.1%
Baseline IGA			
Moderate (444, 222)	-16.8	-14.4	-2.5%
Severe (51, 34)	-26.9	-13.9	-13.1%
Overall	**-18.4**	**-14.5**	**-3.9%**



* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Note: LS Means are presented in this plot. Difference and 95% CI based on ANCOVA model with treatment and analysis center as factors, and baseline value as covariate.
Abbreviations: FMX103: Minocycline Foam, 1.5%; CI: Confidence Interval; n[FMX] = subgroup sample size for active arm, n[V] = subgroup sample size for vehicle arm
Source: Statistical Reviewer's Analysis

8.1.1.9. Center

Trial FX2016-11 enrolled and randomized 651 subjects from 54 centers that were combined to 20 analysis centers. Trial FX2016-12 enrolled and randomized 651 subjects from 46 centers that were combined into 18 analysis centers. All centers were located in the US.

As noted in Section 8.1.1.2, the SAPs specified analyzing the analysis center-by-treatment interaction using the Breslow Day test for the IGA success endpoint and assessing the analysis center-by-treatment interaction in the ANCOVA model for the inflammatory lesion count endpoint using an alpha level of 0.1. The analysis center-by-treatment interaction was statistically significant at the 0.1 level for the inflammatory lesion count endpoint at Week 12 in Trial FX2016-12 only. Since pooling centers could mask center effects, the statistical reviewer repeated the above analyses for the investigational centers (i.e., before pooling) instead of analysis centers (i.e., after pooling). The center-by-treatment interaction remained statistically significant at the 0.1 level for the inflammatory lesion count endpoint at Week 12 in Trial FX2016-12. Therefore, efficacy by center was further explored through plots and descriptive statistics.

Figure 12 through Figure 15 present the results for the coprimary endpoints at Week 12 by center for Trials FX2016-11 and FX2016-12. Only centers that enrolled at least 12 subjects are included in the figures for ease of view. The centers are ordered in descending order based on

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their sample sizes, starting from that with the largest sample size to that with the smallest sample size. There is variation in efficacy by center as seen in the figures. The statistical reviewer conducted a sensitivity analysis where centers were removed one-by-one from the primary analysis to investigate their impact on the overall results. The results showed that no single center drove the overall efficacy results. The large number of centers and small number of subjects per treatment arm in most centers likely describes the large variation. The centers with higher numbers of subjects per treatment arm tended to have more consistent treatment effects with the observed overall treatment effect.

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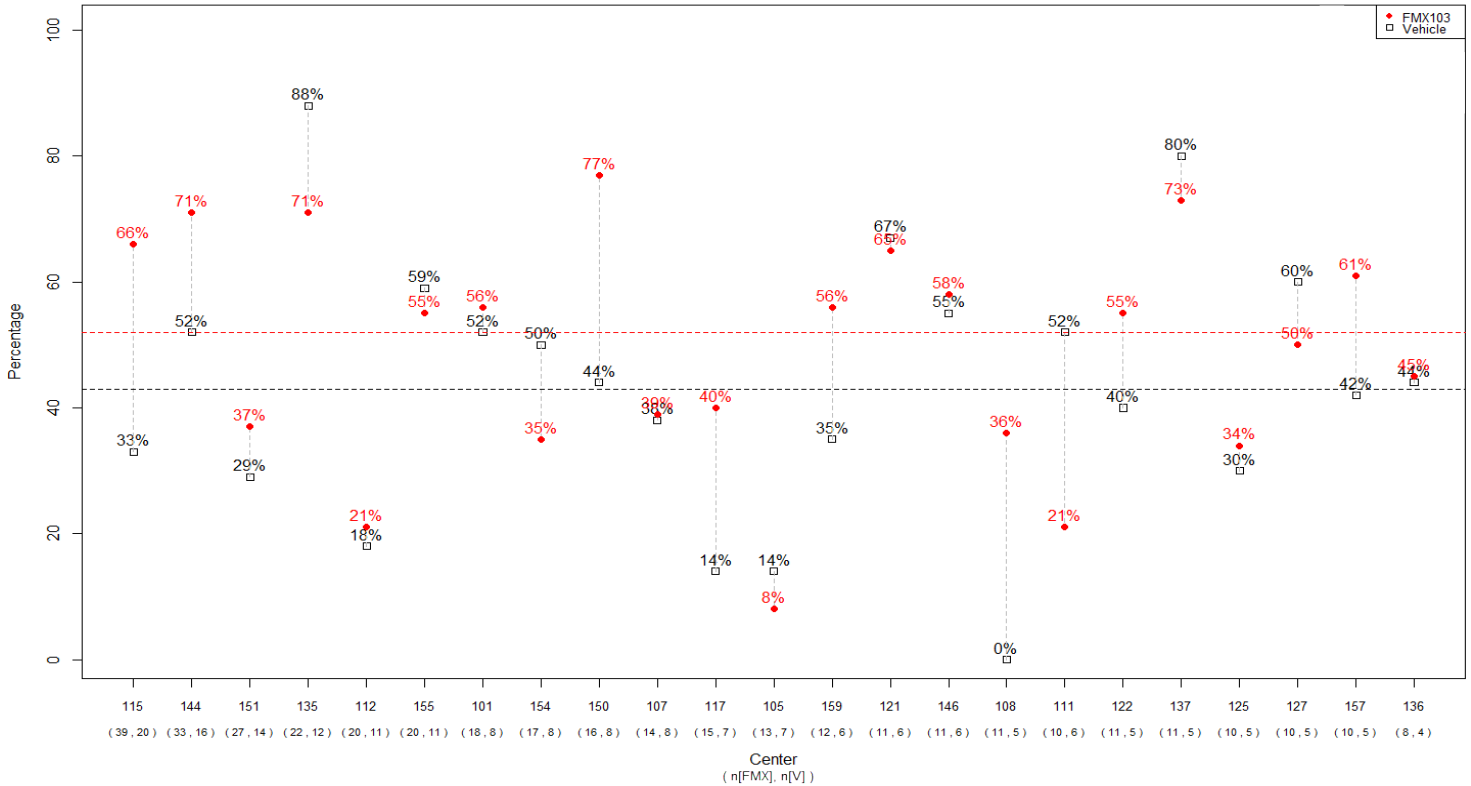
Figure 12: IGA Success at Week 12 by Center for Trial FX2016-11 (ITT; MI*)



* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Note: The dotted horizontal line denotes the overall for each treatment arm.
Abbreviations: n[FMX] = sample size for active arm, n[V] = sample size for vehicle arm
Source: Statistical Reviewer's Analysis

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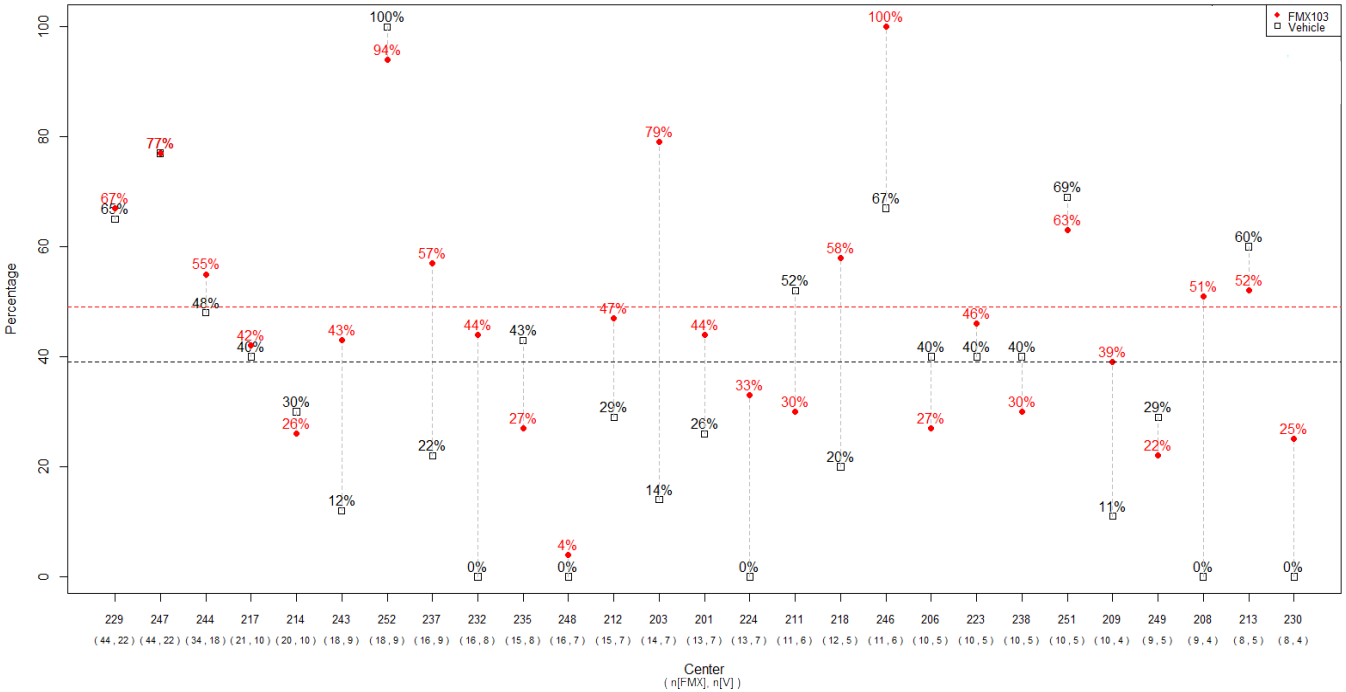
Figure 13: IGA Success at Week 12 by Center for Trial FX2016-12 (ITT; MI*)



* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Note: The dotted horizontal line denotes the overall for each treatment arm.
Abbreviations: n[FMX] = sample size for active arm, n[V] = sample size for vehicle arm
Source: Statistical Reviewer's Analysis

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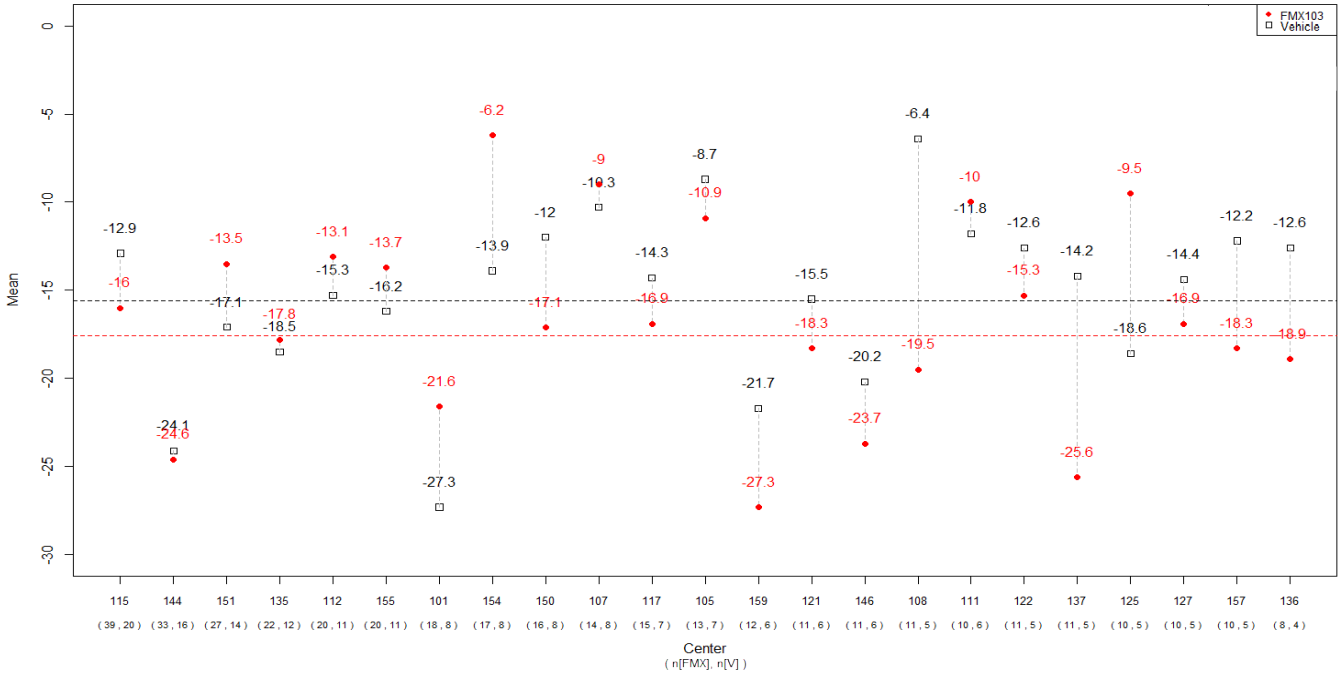
Figure 14: Absolute Change in Inflammatory Lesion Counts at Week 12 by Center for Trial FX2016-11 (ITT; MI*)



* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Note: The dotted horizontal line denotes the overall for each treatment arm.
Abbreviations: n[FMX] = sample size for active arm, n[V] = sample size for vehicle arm
Source: Statistical Reviewer's Analysis

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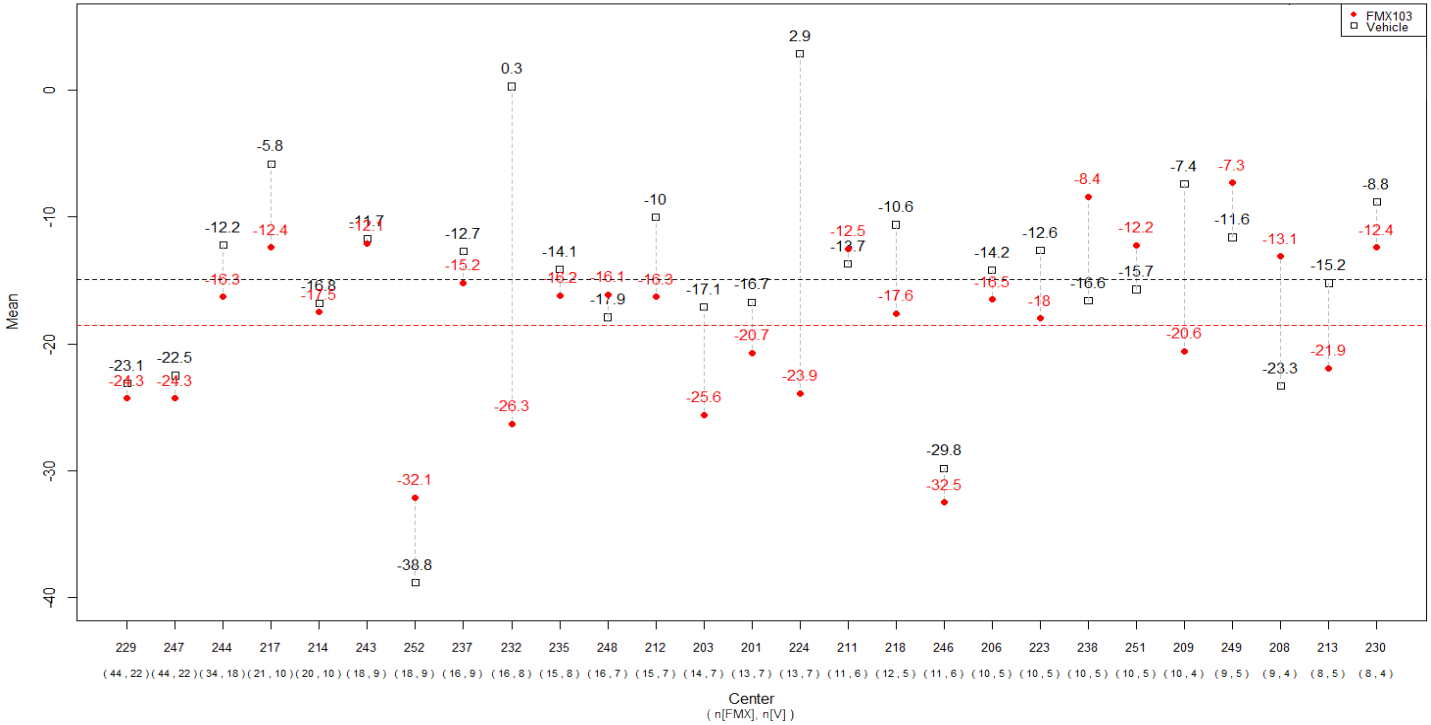
Figure 15: Absolute Change in Inflammatory Lesion Counts at Week 12 by Center for Trial FX2016-12 (ITT; MI*)



* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Note: The dotted horizontal line denotes the overall for each treatment arm.
Abbreviations: n[FMX] = sample size for active arm, n[V] = sample size for vehicle arm
Source: Statistical Reviewer's Analysis

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8.1.2. Phase 2 Trial FX2015-10

8.1.2.1. Trial Design and Endpoints

Trial FX2015-10 was a randomized, multicenter, double-blind, vehicle-controlled, dose-ranging Phase 2 trial to evaluate the safety and efficacy of two different doses of minocycline foam compared to vehicle in the treatment of inflammatory lesions of rosacea.

The following were the key inclusion criteria for the trial:

- Male or female ≥18 years-of-age
- Moderate to severe rosacea per the IGA score (see Table 18) on the proposed facial treatment area consisting of at least 12 facial papules and pustules, excluding lesions involving the eyes and scalp
- Subject diagnosed with rosacea for at least 6 months prior to screening

Table 18: Investigator Global Assessment (IGA) Scale for Trial FX2015-10

Grade	Score	Description
Clear	0	No inflammatory papules or pustules
Almost clear	1	1 or 2 inflammatory papules or pustules
Mild	2	3-11 inflammatory papules or pustules
Moderate	3	12 to 19 inflammatory papules or pustules and no nodules
Severe	4	≥ 20 inflammatory papules or pustules, and up to 2 nodules

The CRFs will allow investigators to report lesions worsening beyond Grade 4 with treatment

Source: Applicant's Protocol FX2015-10

The protocol specified enrolling and randomizing approximately 210 subjects from approximately 14-16 centers in Germany in a 1:1:1 ratio to the following treatment arms:

- Minocycline foam, 1.5% (N=70)
- Minocycline foam, 3% (N=70)
- Vehicle foam (N=70)

Subjects were instructed to apply the study drug topically once daily for 12 weeks. Subjects were advised to use the study drug at approximately the same time each day in the evening. Subjects returned for visits at Weeks 2, 4, 8, 12, and 16. Efficacy evaluations were performed at baseline and Weeks 2, 4, 8, and 12 during the study.

According to the protocol, the primary efficacy endpoint was the absolute change from baseline in inflammatory lesion count at Week 12.

The protocol specified the following secondary efficacy endpoints:

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- The dichotomized IGA score, where success is defined as a two-grade improvement from baseline in IGA score at Week 12
- The dichotomized IGA score, where success is defined as a two-grade improvement from baseline resulting in a 0 or 1 score at Week 12
- Percent change from baseline in inflammatory lesion count at Week 12
- The dichotomized modified IGA (mIGA) score where success is defined as a two-grade improvement from baseline resulting in a 0 or 1 score at Week 12; see Table 19 for the mIGA scale

Table 19: Modified IGA (mIGA) Scale for Trial FX2015-10

Grade	Score	Description
Clear	0	No inflammatory papules or pustules and no erythema
Almost clear	1	1 or 2 inflammatory papules or pustules and residual to mild erythema
Mild	2	3-11 inflammatory papules or pustules and mild erythema
Moderate	3	12 to 19 inflammatory papules or pustules and no nodules and moderate erythema
Severe	4	≥ 20 inflammatory papules or pustules, and up to 2 nodules and severe erythema

The CRFs will allow investigators to report lesions worsening beyond Grade 4 with treatment
Source: Applicant's Protocol FX2015-10

8.1.2.2. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial FX2015-10 enrolled and randomized a total of 233 subjects. One subject was randomized in error and did not have all data collected at baseline. This subject was not included in the ITT population, defined as all randomized subjects. Table 20 presents the disposition of subjects for the ITT population. The most common reason for discontinuation was 'subject request.'

Table 20: Subject Disposition for Trial FX2015-10 (ITT)*

	Minocycline Foam, 1.5% N=79	Minocycline Foam, 3% N=75	Vehicle Foam N=78
Completed	77 (97%)	65 (87%)	71 (91%)
Discontinued	2 (3%)	10 (13%)	7 (9%)
Reasons of discontinuation			
Adverse event	0 (0%)	3 (4%)	1(1%)
Lost to follow-up	1 (1%)	0 (0%)	0 (0%)
Subject request	1 (1%)	6 (8%)	3 (4%)
Protocol deviation	0 (0%)	1 (1%)	1 (1%)
Other	0 (0%)	0 (0%)	2 (3%)

* Intent-to-treat (ITT) population is defined as all randomized subjects
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

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The demographics for Trial FX2015-10 are presented in Table 21. The demographics were generally balanced across the treatment arms. The majority of the subjects were female (approximately 60%) and white (approximately 99%).

Table 21: Demographics for Trial FX2016-10 (ITT*)

	Minocycline Foam, 1.5% N=79	Minocycline Foam, 3% N=75	Vehicle Foam N=78
Age (years)			
Mean (SD)	51.2 (15.3)	51.6 (14.1)	54.8 (14.0)
Median	51	52	53.5
Range	21 – 82	22 – 78	24 – 80
18 – 40	18 (23%)	14 (19%)	12 (15%)
41 – 64	44 (56%)	45 (60%)	44 (56%)
≥65	17 (21%)	16 (21%)	22 (28%)
Sex			
Male	26 (33%)	24 (32%)	37 (47%)
Female	53 (67%)	51 (68%)	41 (53%)
Race			
White	78 (99%)	73 (97%)	78 (100%)
Asian	0 (0%)	1 (1%)	0 (0%)
Hispanic or Latino	0 (0%)	1 (1%)	0 (0%)
Other	1 (1%)	0 (0%)	0 (0%)

*Intent-to-treat (ITT) population is defined as all randomized subjects
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis);

Table 22 presents the baseline disease characteristics for Trial FX2015-10. The baseline disease characteristics were generally balanced across the treatment arms. Approximately half of the subjects were enrolled with a baseline IGA score of 3 (moderate).

Table 22: Baseline Disease Characteristics for Trial FX2015-10 (ITT*)

	Minocycline Foam, 1.5% N=79	Minocycline Foam, 3% N=75	Vehicle Foam N=78
IGA			
3 – Moderate	34 (43%)	29 (39%)	40 (51%)
4 – Severe	45 (57%)	46 (61%)	38 (49%)
Inflammatory Lesions			
Mean (SD)	34.5 (20.9)	34.1 (25.0)	30.6 (15.5)
Median	28	27	26
Range	13 – 125	12 – 189	12 – 91
t <15	4 (5%)	7 (9%)	4 (5%)
15 – 75	71 (90%)	64 (85%)	73 (94%)
>75	4 (5%)	4 (5%)	1 (1%)

*Intent-to-treat (ITT) population is defined as all randomized subjects
Abbreviations: IGA = Investigator's Global Assessment; SD = standard deviation
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

8.1.2.3. Efficacy Results

Table 23 presents the results for the primary and secondary endpoints in Trial FX2015-10 using the ITT population and the MI method for handling the missing data.

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Table 23: Efficacy Results for Trial FX2015-10 (ITT; MI*)

Type	Endpoint	Minocycline 1.5% (N=79)	Minocycline 3% (N=75)	Vehicle (N=78)
Primary	**Absolute Change in Inflammatory Lesions**			
	Mean	-21.1	-19.9	-7.8
	Median	-17.8	-14	-8.3
	Range	-95 – 12.2	-129 – 11.9	-48 – 96
	LS Mean	-21.2	-20.3	-9.9
	P-value(1)	<0.001	<0.001	
Secondary	**2-grade Improvement on IGA**	41%	34%	19%
	P-value(2)	0.001	0.027	
	IGA Score of 0 or 1	26%	19%	8%
	P-Value(2)	0.0006	0.0356	
	Percent Change in Inflammatory Lesions			
	Mean	-61.4%	-55.5%	-29.7%
	Median	-69.9%	-63.2%	-37.1%
	Range	-100 – 45.2	-100 – 65.3	-100 – 165.5
	LS Mean	-64.5%	-58.5%	-32.0%
	P-value(1)	<0.001	<0.001	

* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 10 imputed datasets)
(1) P-value based on an analysis of covariance with treatment, baseline value and analysis center (after pooling) in the model
(2) P-value based on a CMH test stratified by analysis center (after pooling)
Abbreviations: IGA = Investigator Global Assessment; ITT = intent-to-treat; LS Mean = least squares mean
Source: Statistical Reviewer's Analysis (slightly different than the Applicant's Analysis)

8.1.2.4. Comparison Between Phase 2 and Phase 3 Results

Table 24 presents the efficacy results for the two Phase 3 trials (FX2016-11/12) and the Phase 2 trial (FX2015-10). We observe that the IGA success rates were lower for both arms in Trial FX2015-10 compared to the Phase 3 trials; however, the treatment effect was similar in all trials. The lower IGA success rates can be due to the fact that the Phase 2 Trial FX2015-10 enrolled a higher proportion of subjects with baseline IGA score of 4 compared to the Phase 3 trials.

For the Inflammatory lesion count, the *mean* change from baseline was about two times lower for the vehicle arm in Phase 2 Trial FX2015-10 compared to the vehicle arm in the Phase 3 trials. However, the Phase 2 Trial FX2015-10 enrolled subjects with a wider range of inflammatory lesion count (~12-189 lesions) compared to the Phase 3 trials (~15-75 lesions). The statistical reviewer explored the change in inflammatory lesion count in Trial FX2015-10 for the subgroup of subjects with baseline number of inflammatory lesions between 15-75. The results are presented in Table 25, along with the results for the Phase 3 trials.

The treatment effect remained higher in Trial FX2015-10 compared to the Phase 3 trials. Differences in the population between the Phase 2 trial (FX2015-10) and the Phase 3 trials (FX2016-11/12) could have contributed to the higher treatment effect in the inflammatory lesion count. The Phase 2 trial was conducted in Germany, while the Phase 3 trials were conducted in the US. The Phase 3 trials enrolled subjects with "no more than 2 nodules on the face", while there was no such enrollment criterion for the Phase 2 trial. The Phase 3 trials

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enrolled a slightly higher proportion of female (~70%) subjects compared to the Phase 2 trial (~60%).

Table 24: Efficacy Results for Trials FX2016-11, FX2016-12 and FX2015-10 (ITT; MI*)

	Trial FX2016-11		Trial FX2016-12		Trial FX2015-10	
Endpoint	**Minocycline Foam N=495**	**Vehicle Foam N=256**	**Minocycline Foam, 1.5% N=514**	**Vehicle Foam N=257**	**Minocycline Foam, 1.5% N=79**	**Vehicle Foam N=78**
IGA Success**	52%	43%	49%	39%	26%	19%
Treatment difference(1)	9%		10%		7%	
Inflammatory Lesions Absolute change from baseline						
LS mean(2)	-17.6	-15.4	-18.4	-14.5	-21.2	-9.9
Treatment difference(2)	-2.2		-3.9		-11.3	
Percent change from baseline						
LS Mean(2)	-61.3%	-54.1%	-60.2%	-48.9%	-64.5%	-32.0%
Treatment difference(2)	-7.3%		-11.3%		32.5%	

* Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 10 imputed datasets)
**IGA Success is defined as an IGA score of 0 or 1 and at least a 2-grade improvement from baseline
(1) Treatment Difference is based on the CMH test stratified by analysis center
(2) LS Means and Treatment Difference are based on ANCOVA model with treatment, baseline value and analysis center in the model
Abbreviations: IGA = Investigator Global Assessment; LS Means = least squares means; ITT = intent-to-treat; CMH = Cochran-Mantel-Haenszel

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Table 25: Results for Inflammatory Lesion Count for Trials FX2016-11, FX2016-12 and FX2015-10 for Subjects With Baseline Inflammatory Lesions Ranging From 15-75 (ITT; MI*)

	Trial FX2016-11		Trial FX2016-12		Trial FX2015-10	
Inflammatory Lesions	**Minocycline Foam N=495**	**Vehicle Foam N=256**	**Minocycline Foam, 1.5% N=514**	**Vehicle Foam N=257**	**Minocycline Foam, 1.5% N=79**	**Vehicle Foam N=78**
Absolute change from baseline						
LS Mean change	-17.6	-15.4	-18.4	-14.5	-20.8	-8.8
Treatment difference	-2.2		-3.9		-11.9	
15-24 lesions at baseline	N=238 (48%)	N=121 (47%)	N=236 (46%)	N=107 (42%)	N=23 (32%)	N=31 (42%)
LS Mean change	-11.7	-10.9	-11.6	-10.8	-15.0	-8.6
Treatment difference	-0.8		-0.8		-6.5	
25-49 lesions at baseline	N=219 (44%)	N=116 (45%)	N=232 (45%)	N=124 (48%)	N=38 (53%)	N=35 (48%)
LS Mean change	-20.9	-17.4	-20.4	-14.9	-19.3	-9.7
Treatment difference	-3.5		-5.5		-9.5	
50-75 lesions at baseline	N=37 (7%)	19 (7%)	N=46 (9%)	N=26 (10%)	N=10 (14%)	N=7 (10%)
LS Mean change	-36.8	-34.9	-37.9	-30.0	-49.7	-11.8
Treatment difference	-1.9		-7.9		-37.9	
Percent change from baseline						
LS Mean change	-61.3%	-54.1%	-60.2%	-48.9%	-64.3%	-31.9%
Treatment difference	-7.3%		-11.3%		-32.3%	
15-24 lesions at baseline	N=238 (48%)	N=121 (47%)	N=236 (46%)	N=107 (42%)	N=23 (32%)	N=31 (42%)
LS Mean change	-59.1%	-54.0%	57.9%	-54.1%	-75.6%	-42.3%
Treatment difference	-5.1%		-3.9%		-33.3%	
25-49 lesions at baseline	N=219 (44%)	N=116 (45%)	N=232 (45%)	N=124 (48%)	N=38 (53%)	N=35 (48%)
LS Mean change	-64.1%	-54.0%	-61.2%	-43.6%	-57.4%	-29.4%
Treatment difference	-10.1%		-17.6%		-28.0%	
50-75 lesions at baseline	N=37 (7%)	19 (7%)	N=46 (9%)	N=26 (10%)	N=10 (14%)	N=7 (10%)
LS Mean change	-61.1%	-56.4%	-63.4%	-51.7%	-78.8%	-16.3%
Treatment difference	-4.6%		-11.7%		-61.9%	

*Intent-to-treat (ITT) population is defined as all randomized subjects. Missing data imputed using multiple imputation (MI; 100 imputed datasets)
Note: LS Means and Treatment Difference are based on ANCOVA model with treatment, baseline value and analysis center in the model

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8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety for minocycline foam, 1.5% for the treatment of inflammatory lesions of rosacea focuses on pooled data from Phase 2 trial FX2015-10 and Phase 3 trials FX2016-11 and FX2016-12. Trials FX2016-11 and FX2016-12 were Phase 3, multicenter, randomized, double-blind, vehicle-controlled, 2-arm safety and efficacy trials of identical design. Trial FX2015-10 was a Phase 2, multicenter, double-blind, vehicle-controlled, randomized, dose ranging trial. The trials included a double-blind treatment period of 12 weeks. Because the study designs are similar, subjects from the vehicle and minocycline foam, 1.5% treatment arms of trial FX2015-10 will be included in the primary safety analysis.

The Phase 3 trial population included a total of 1521 subjects ≥18 years of age with moderate to severe papulopustular rosacea with 15-75 facial papules and pustules, ≤2 nodules, IGA score 3 or 4, and a history of erythema or flushing of face. Subjects were randomized 2:1 to treatment with minocycline foam, 1.5% or vehicle foam.

The Phase 2 trial included 232 subjects ≥18 years of age with moderate to severe papulopustular rosacea (≥12 facial papules and pustules and IGA score of 3 or 4) who were randomized 1:1:1 to treatment with minocycline foam 1.5%, minocycline foam 3%, or vehicle foam. During the Phase 2 trial, 157 subjects were randomized to minocycline foam, 1.5% or vehicle.

In all 3 trials, subjects applied minocycline foam, 1.5% or vehicle foam to the entire face once daily. Investigators conducted safety and efficacy assessments at baseline followed by Weeks 2, 4, 8, and 12. The safety population as defined and discussed in the next section of this review included 1087 subjects treated with minocycline foam, 1.5%.

The Applicant submitted long-term safety data from Study FX2016-13, which was a 40-week, open-label extension to the Phase 3 trial. Subjects applied minocycline foam, 1.5% once daily as necessary.

The Applicant also submitted supportive safety data from two PK/Bioavailability studies conducted under conditions of maximal use, as well as four dermal safety studies. It should be noted that one of the maximal use PK studies and all dermal safety studies were conducted using AMZEEQ (minocycline) topical foam, 4%. As previously discussed, the formulations of the 4% product and the 1.5% product are identical except for the concentration of the active ingredient.

To determine the safety profile of minocycline foam, 1.5%, the review team analyzed the following types of pooled data: exposure, demographics, baseline characteristics, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, laboratory results, vital signs, and findings from physical examinations.

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8.2.2. Review of the Safety Database

Overall Exposure

The primary analysis dataset for the review of safety for minocycline foam, 1.5% included pooled data from Phase 3 trials FX2016-11 and FX2016-12 as well as Phase 2 trial FX2015-10. Data from the other studies were not integrated because of dissimilar study designs and different dose regimens.

The Phase 2/3 safety population includes all randomized subjects who received at least one dose of the study medication during double-blind treatment in the Phase 2 and Phase 3 trials. Safety data from this population were analyzed according to the treatment that subjects received. For Phase 3 trial FX2016-12, the intent-to-treat (ITT) and safety populations were identical (N=771). The ITT and safety populations for Phase 2 trial FX2015-10 were also identical (N=157 in minocycline foam, 1.5% and vehicle arms). For Phase 3 trial FX2016-11, the ITT (N=751) and Safety (N=750) populations were slightly different. One subject was randomized, but never dosed, and was therefore included in the ITT population but excluded from the safety population. The combined Phase 2/3 safety population by trial and treatment arm is presented in the table below.

Table 26: Combined Phase 2/3 Safety Population

Study Identifier	Minocycline Foam 1.5%	Vehicle Foam	Subjects
FX2015-10	79	78	157
FX2016-11	494	256	750
FX2016-12	514	257	771
Total	1087	591	1678

Source: Reviewer's Table created in JReview using ISS and FX2015-10 dataset

Subjects enrolled in the Phase 3 trials had the option to enroll in Trial FX2016-13, which was a 40-week open-label extension. Of the 1087 subjects in the combined Phase 2/3 safety population exposed to minocycline foam, 1.5%, a total of 993 were exposed for at least 12 weeks, 465 for more than 6 months (168 days), and 272 for more than 1 year (350 days).

For the Phase 3 trials, the Applicant summarized exposure by treatment duration in days as well as by the amount of study drug applied (grams/day). The mean treatment duration in subjects treated with minocycline foam, 1.5% was 82.5 days and the mean amount of study drug applied per day was 0.78 grams. The exposure was similar for vehicle foam. In Phase 2 trial FX2015-10, the mean treatment duration in subjects treated with minocycline foam, 1.5% was 84.8 days and the mean amount of study drug applied was 0.36 grams/day (vs. 80.7 days and 0.39 grams/day in the vehicle group).

In the open-label extension study, the overall mean (SD) number of days of exposure to minocycline foam, 1.5% during the open-label study was 248.2 (65.46) days. The mean [SD] exposure was higher in the subjects who were treated with minocycline foam, 1.5% during the double-blind period in the feeder studies (251.3 [60.69] days) than in the subjects who were treated with vehicle (242.1 [73.61] days).

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Relevant characteristics of the safety population

The demographics of the safety population are similar to the ITT population. In the combined Phase 2/3 safety population, the majority of subjects were white (96.5%), female (69.5%), and between 40-64 years of age (60.7%). A total of 278 (16.6%) were 65 years of age or older. The demographic characteristics of both treatment groups were comparable. In the Phase 3 trials, most subjects were non-Hispanic or Latino (66.7%); ethnicity information was not reported for Phase 2 trial FX2015-10 which was conducted in Germany. Refer to Appendix 14.5 for demographic characteristics of subjects in the safety population.

Adequacy of the safety database:

The total subject exposure to minocycline foam, 1.5% applied daily for 12 weeks provides adequate data for the evaluation of safety. The total exposures for 6 months and 1 year are sufficient to characterize the safety of the product over longer treatment periods. The demographics of the study population are sufficiently representative of the target population. Therefore, the safety database submitted by the Applicant is sufficient to characterize the safety profile of minocycline foam, 1.5% for the treatment of inflammatory lesions of rosacea.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of minocycline foam, 1.5% for the treatment of inflammatory lesions of rosacea in adult population. Data quality and fitness were evaluated in conjunction with the CoreDF team. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

An adverse event (AE) was defined as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related." AE' s included laboratory findings or results of other diagnostic procedures that were considered to be clinically significant (e.g., that required unscheduled diagnostic procedures or treatment measures or resulted in withdrawal from the study). No causal relationship with the study drug was implied by the use of the term "adverse event." A TEAE was defined as "any AE with an onset date on or after the first application of study drug, and before the last application of study drug plus 3 days, having been absent pre-treatment or worsening relative to the pre-treatment state." TEAEs form the primary basis of the review of safety.

All AEs were recorded at each visit as reported spontaneously by the subject or observed by the investigator. Subjects were asked whether, since the time of the last observation or visit, they had:

- Experienced any changes in well-being
- Used any new medications

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- Changed medication regimens (both prescription and over-the-counter)
- Been admitted to a hospital or had any accidents
- Developed unusual headaches or changes in vision

Except for the last item above, all questions were of a general nature and did not suggest symptoms.

Investigators recorded in the case report from the date the AE began and ended or that the AE was ongoing. Also recorded were the severity, relationship to the use of study drug, and action taken or outcome. Investigators categorized the severity of the AE according to the following criteria:

- Mild: The symptom had a negligible effect or no impairing effect on the subject's normal function.
- Moderate: The symptom impaired the subject's normal function to some extent.
- Severe: The symptom had an obvious, significantly impairing effect on the subject's normal function.

Investigators also assessed the relationship of the AE to treatment with study drug using the following criteria:

- Unlikely: There was no medical evidence to suggest that the AE may have been related to study drug usage, or there was another more probable medical explanation.
- Possible: There was medical evidence to suggest that there was a reasonable possibility that the AE may have been related to study drug usage. However, other medical explanations could not be excluded as a possible cause.
- Probable: There was strong medical evidence to suggest that the AE was related to study drug usage.

SAE was defined as an AE that met one of the following criteria:

- Fatal
- Life-threatening
- Significantly or permanently disabling
- A congenital anomaly or birth defect in the offspring of a subject
- Requiring in-patient hospitalization or prolonging a current hospitalization
- A medically important event that jeopardized the subject or required medical or surgical intervention to prevent one of the outcomes listed in this definition

Adverse events that were ongoing when a subject withdrew from or completed the study were followed until resolution or stabilization, or for 30 days, whichever was shorter. Subjects who experienced any clinically significant AE remained under medical supervision until the investigator or the Applicant's medical monitor deemed the AE resolved, stabilized, or was no longer serious enough to warrant follow-up.

Laboratory values that were abnormal and not assessed as AEs were followed at the discretion of the investigator or the Applicant's medical monitor until resolved or stabilized. Although

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pregnancy was not considered an AE, such subjects were withdrawn from the study and followed until the outcome of the pregnancy was known.

Routine Clinical Tests

Investigators conducted safety assessments at baseline followed by Weeks 2, 4, 8, and 12 during the Phase 2 and Phase 3 trials. During the open-label extension study, subjects returned for clinic visits at Week 4, then every 6 weeks thereafter. The evaluation of safety included vital signs (blood pressure and heart rate), local skin tolerability assessments (erythema, telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and hyperpigmentation at the sites [facial] of study drug application as assessed by the investigator), and general physical examinations.

Investigators conducted clinical laboratory testing at Screening and Week 12 during the Phase 2 and Phase 3 trials, as well as at Week 16 and 40 during the open-label extension study. Laboratory assessments included hematology, serum chemistry, and urinalysis. During the Phase 2 trial, serum pregnancy tests were performed on all females of reproductive potential at Screening and Week 12; urine pregnancy tests (UPTs) were performed at baseline and Week 2, 4, and 8. During the Phase 3 trials, UPTs were performed at baseline and Week 4, 8, and 12. During the open-label extension study, UPTs were performed at all study visits and when a subject prematurely withdrew from the study. In addition, home pregnancy tests were dispensed at each study visit to all female subjects of reproductive potential and were to be performed at least monthly and whenever there was a suspicion of pregnancy (e.g., a missed or late menstrual period).

During the Phase 3 trials, the Applicant conducted active assessments of local skin tolerability at each study visit. Telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and skin hyperpigmentation were scored on a scale of 0 (“none”), 1 (“mild”), 2 (“moderate”), or 3 (“severe”). Erythema was scored on a scale of 0 (“clear”), 1 (“almost clear”), 2 (“mild”), 3 (“moderate”), or 4 (“severe”). During the Phase 2 Trial, the active assessments of local skin safety at each study visit included telangiectasia, burning/stinging, and flushing/blushing. These were scored on a scale of 0 (“none”), 1 (“mild”), 2 (“moderate”), or 3 (“severe”).

8.2.4. Safety Results

Deaths

Two deaths occurred during the development program for minocycline foam, 1.5%. One occurred during Phase 3 trial FX2016-11 and one during the open-label extension Study FX2016-13. Brief narrative summaries for these subjects are provided below.

- Study FX2016-11: A 46 year old female (Subject (b) (6)) with history of asthma randomized to vehicle foam died subsequent to a myocardial infarction. The last dose of study drug was applied (b) (6) (Day 7) and the fatal event occurred on Day 10. The

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investigator considered this event to be severe and unrelated to study drug. I concur with the investigator's assessment that this event was unrelated to treatment.

- Study FX2016-13: A 48 year old male (Subject (b) (6)) with a history of hypercholesterolemia died from an unknown cause. He applied one dose of minocycline foam, 1.5% on (b) (6) (Day1). The site was informed by the subject's mother and sister that he was found dead in his apartment and the cause of death was unknown. No further information was available. No other AEs were reported for this subject. This was not considered a treatment-emergent SAE as his last treatment date was (b) (6) and the fatal SAE occurred on (b) (6). The investigator considered this event to be severe and unrelated to study drug. I concur with the investigator's assessment that this event was unrelated to treatment.

Serious Adverse Events

In the Phase 2/3 safety population, 5 (0.5%) subjects treated with minocycline foam, 1.5% experienced 12 SAEs and 6 (1.0%) subjects treated with vehicle experienced 10 SAEs. These SAEs are presented in the table below:

Table 27:Treatment-Emergent SAEs, Phase 2/3 Safety Population

Body System or Organ Class	Preferred Term	Minocycline Foam 1.5% (n=1087)	Vehicle Foam (n=591)
Cardiac disorders	Myocardial infarction	0 (0.0%)	1 (0.2%)
	Tachycardia	0 (0.0%)	1 (0.2%)
Gastrointestinal disorders	Gastrointestinal hemorrhage	0 (0.0%)	1 (0.2%)
	Nausea	1 (0.1%)	0 (0.0%)
General disorders and administration site conditions	Chest discomfort	1 (0.1%)	0 (0.0%)
	Chest pain	0 (0.0%)	1 (0.2%)
	Fatigue	1 (0.1%)	0 (0.0%)
	Pyrexia	0 (0.0%)	1 (0.2%)
Immune system disorders	Seasonal allergy	1 (0.1%)	0 (0.0%)
Infections and infestations	Gastroenteritis	0 (0.0%)	1 (0.2%)
Injury, poisoning and procedural complications	Contusion	1 (0.1%)	0 (0.0%)
Metabolism and nutrition disorders	Dehydration	1 (0.1%)	0 (0.0%)
Nervous system disorders	Cerebral hemorrhage	1 (0.1%)	0 (0.0%)
	Hemiparesis	1 (0.1%)	0 (0.0%)
	Syncope	1 (0.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Asthma	0 (0.0%)	1 (0.2%)
	Dyspnea	1 (0.1%)	1 (0.2%)
	Pulmonary embolism	1 (0.1%)	0 (0.0%)
Vascular disorders	Hypertension	1 (0.1%)	1 (0.2%)
	Subjects	**5 (0.5%)**	**6 (1.0%)**
	Events	**12**	**10**

Abbreviation: SAE = serious adverse event
Source: Reviewer's Table created in JReview using FX2010-15, FX2016-11, and FX2016-12 datasets

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One subject treated with minocycline foam, 1.5% had 3 SAEs classified as severe intensity (cerebral hemorrhage, hemiparesis, and pulmonary embolism); 4 subjects treated with vehicle had 5 SAEs classified as severe intensity (myocardial infarction, pyrexia, gastroenteritis, asthma, and dyspnea). Other than the fatal SAE of myocardial infarction, no SAEs led to discontinuation of treatment.

During the open-label extension Study FX2016-13, a total of 13 (2.6%) subjects overall experienced 15 SAEs. Investigators considered the SAEs to be treatment-emergent in 10 (2.0%) of subjects. In the remaining 3 subjects, the SAEs occurred more than 3 days after the most recent application of minocycline foam, 1.5%. Investigators classified a total of 9 treatment-emergent SAEs as severe intensity: pneumonia, malignant melanoma, death, periorbital cellulitis, staphylococcal infection, labyrinthitis, post-procedural hemorrhage, chronic obstructive pulmonary disease, and appendicitis perforated.

Overall, SAEs were uncommon in the Phase 2/3 safety population and during the open-label extension study. There was no imbalance in SAEs between minocycline foam, 1.5% and vehicle foam in the Phase 2/3 safety population. Investigators considered none of the SAEs to be related to study drug; I concur with the investigator's assessment. No SAEs were reported during the Phase 1 studies.

Narrative summaries of fatal SAEs were provided above. The remaining narratives of subjects treated with minocycline foam, 1.5% who experienced SAEs are presented in Appendix 14.5 of this review. Brief summaries of the narratives are presented below:

<u>Trial FX2015-10</u>

A 60 y/o female (Subject (b) (6)) was noted at Screening to have a contusion (moderate bruising of the head secondary to a fall) which required hospitalization. Action taken with study drug was not applicable as the SAE occurred prior to treatment with study drug. The investigator assessed the AE of contusion as unrelated to study drug administration.

A 75 y/o male (Subject (b) (6)) experienced SAEs of cerebral hemorrhage, pulmonary embolism, and hemiparesis requiring hospitalization in the intensive care unit. The event occurred during the follow-up period and the subject applied his last dose of study drug 4 days prior to the event. The investigator assessed the cerebral hemorrhage, pulmonary embolism, and hemiparesis as unrelated to study drug administration.

<u>Trial FX2016-11</u>

A 63 y/o female (Subject (b) (6)) experienced syncope requiring hospitalization. No action was taken with the study drug, and the event resolved. The investigator considered the relationship to study drug as unlikely.

A 51 y/o female (Subject (b) (6)) experienced shortness of breath, nausea, fatigue, chest discomfort, and dehydration and was hospitalized. No action was taken with the study drug, and the SAEs resolved. The investigator considered all of the events to be unlikely related to the study drug.

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Trial FX2016-12

A 66 y/o female (Subject (b) (6)) experienced uncontrolled hypertension and was hospitalized. No action was taken with the study drug, and the SAE resolved. The investigator considered the relationship to study drug as unlikely.

Trial FX2016-13

A 62 y/o female (Subject (b) (6)) experienced pneumonia and was hospitalized and treated with IV antibiotics. Study drug was interrupted, and the SAE resolved. The investigator considered the relationship to the study drug as unlikely.

A 25 y/o female (Subject (b) (6)) experienced a post procedural hemorrhage after an endometrial biopsy. She was hospitalized in the ICU and required a blood transfusion. Study drug was interrupted and the SAE resolved. The investigator considered the relationship to the study drug as unlikely.

A 46 y/o female (Subject (b) (6)) experienced melanoma which was surgically excised. No action was taken with study drug and the SAE was resolved. The investigator considered the relationship to the study drug as unlikely.

A 34 y/o male (Subject (b) (6)) experienced bilateral subdural hematomas and cerebrospinal fluid (CSF) leak which were surgically repaired. The subject withdrew consent and the SAEs resolved. The investigator considered the relationship of the SAEs to the study drug as unlikely.

A 49 y/o female (Subject (b) (6)) experienced large intestinal obstruction and was hospitalized. No action was taken with study drug and the SAE resolved. The investigator considered the relationship to the study drug as unlikely.

A 62 y/o female (Subject (b) (6)) experienced chronic obstructive pulmonary disease and was hospitalized. Study drug was interrupted and the SAE resolved. The investigator considered the relationship to the study drug as unlikely.

A 63 y/o female (Subject (b) (6)) experienced syncope and was hospitalized. Study drug was interrupted, and the SAE resolved. The investigator considered the relationship to the study drug as unlikely.

A 75 y/o male (Subject (b) (6)) experienced periorbital cellulitis (presumptive Methicillin-resistant Staphylococcus aureus [MRSA]) and was hospitalized and treated with IV antibiotics. Study drug was interrupted and the SAEs resolved. The investigator considered the relationship of the SAEs to the study drug as unlikely.

A 60 y/o male (Subject (b) (6)) experienced labyrinthitis which caused vertigo requiring hospitalization. He was treated with IV fluids, meclizine, and steroids. No action was taken with study drug, and the SAE resolved. The investigator considered the relationship to the study drug as unlikely.

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A 53 y/o male (Subject (b) (6)) experienced a cerebrovascular accident and was hospitalized. No action was taken with the study drug, and the SAE resolved. The investigator considered the relationship to the study drug as unlikely.

A 46 y/o female (Subject (b) (6)) experienced hypokalemia and was hospitalized with heart palpitations. She was treated with potassium replacement. No action was taken with the study drug and the SAE resolved. The investigator considered the relationship to the study drug as unlikely.

A 47 y/o female (Subject (b) (6)) experienced perforated appendicitis with secondary sepsis. She underwent laparoscopic appendectomy and treated with IV antibiotics. Study drug was discontinued (Day 62) and the SAEs resolved. The investigator considered the relationship to the study drug as unlikely.

Dropouts and/or Discontinuations Due to Adverse Effects

In the Phase 2/3 safety population, 7 (7/1087; 0.6%) of subjects treated with minocycline foam, 1.5% and 3 (3/591; 0.5%) of subjects treated with vehicle discontinued treatment because of an AE. Only one of the TEAEs leading to discontinuation was an SAE (fatal myocardial infarction; discussed in the previous section). AEs leading to discontinuation in subjects treated with minocycline foam, 1.5%, and number of subjects affected, are listed below:

- Dermal cyst (1; Trial FX2016-11)
- Influenza (1; Trial FX2016-11)
- Urinary tract infection (1; Trial FX2016-11)
- Dermatitis and pruritus (1; Trial FX2016-11)
- Bladder mass (1: Trial FX2016-11)
- Pruritus (1: Trial FX2016-12)
- Telangiectasia (not treatment-emergent; occurred on Day 1 prior to application of study drug) (1: Trial FX2016-12)

Investigators classified all AE leading to discontinuation as mild or moderate in severity, and all were resolved. Investigators considered the relation to treatment as unlikely, except for the subject in FX2016-12 with pruritus, for which the relationship to treatment was considered probable.

During open-label extension Study FX2016-13, five (5/504; 1.0%) subjects experienced 9 events leading to discontinuation. These are listed below:

- Mydriasis (1 subject)
- Enchondromatosis (1 subject)
- Dermatitis contact (1 subject)
- Rosacea (1 subject)
- Appendicitis perforated, appendectomy, anemia, leukocytosis, and sepsis (1 subject)

Investigators considered the event of perforated appendicitis to be an SAE (refer to narrative in the previous section for further information). Investigators considered the AEs of mydriasis,

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dermatitis contact, and rosacea to be possibly or probably related to treatment.

Narratives of subjects who discontinued because of AEs in the Phase 2/3 safety population and long-term extension Study FX2016-13 are presented in Appendix 14.5 of this review. Brief summaries of the narratives are presented below:

FX2016-11

A 39 y/o male (Subject (b) (6)) experienced a cyst on Day 48 and was discontinued on Day 57. The event resolved. The investigator considered the relationship to study drug as unlikely.

A 64 y/o female (Subject (b) (6)) experienced influenza on Day 50. Her last dose of study drug was Day 53 and she was discontinued on Day 86. The investigator considered the relationship to the study drug as unlikely.

A 65 y/o female (Subject (b) (6)) experienced a UTI on Day 4, received her last dose of study drug on Day 7, and was discontinued on Day 9. The investigator considered the relationship to the study drug as unlikely.

An 81 y/o male (Subject (b) (6)) experienced AEs of inflamed dermatitis and pruritus on his back on Day 20. His last dose of study drug was Day 23 and he was discontinued on Day 59. The investigator considered the relationship to the study drug as unlikely.

A 63 y/o female (Subject (b) (6)) experienced a bladder mass on Day 47. Her last dose of study drug was Day 57 and she was discontinued Day 97. The investigator considered the relationship to the study drug as unlikely.

FX2016-12

A 44 y/o female (Subject (b) (6)) experienced telangiectasia on Day 1, prior to the first application of study drug. Her last dose of study drug was Day 8 and she was discontinued on Day 15. The investigator considered the relationship to the study drug as unlikely.

A 66 y/o male (Subject (b) (6)) experienced pruritus on Day 2. His last dose of study drug was Day 7 and he was discontinued on Day 36. The Investigator considered the relationship to study drug as probable.

FX2016-13

A 49 y/o female (Subject (b) (6)) experienced mydriasis in the left pupil on Day 33. Her last dose of study drug was Day 62 and she was discontinued on Day 92. The Investigator considered the relationship to the study drug as possible.

A 37 y/o female (Subject (b) (6)) experienced enchondromatosis of the femur on Day 71. Her last dose was Day 83 and she was discontinued on Day 168. The investigator considered the relationship to the study drug as unlikely.

A 37 y/o female (Subject (b) (6)) experienced contact dermatitis on Day 81. Her last dose was Day 95 and she was discontinued on Day 149. The Investigator considered the relationship to the study drug as possible.

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A 64 y/o male (Subject (b) (6)) experienced a flare of rosacea on Day 1. His last dose of study drug was Day 15 and he was discontinued on Day 285. The investigator considered the relationship to study drug as probable.

Significant Adverse Events

Human Reproduction and Pregnancy

Because of the risk of fetal harm with tetracycline-class antibiotics when administered to pregnant women, the Applicant required females of reproductive potential to have a negative pregnancy test at screening and to use effective forms of contraception. In addition, during the Phase 3 trials urine pregnancy tests (UPTs) were performed on all females of reproductive potential at baseline; Weeks 4, 8, and 12; or when a subject prematurely withdraws from the study. During the Phase 2 trial, serum pregnancy tests were performed at Screening and Week 12, and UPTs were performed at baseline and Weeks 2, 4, and 8. During the open-label extension study, UPTs were performed at all study visits and when a subject prematurely withdrew from the study. If pregnancy was confirmed, the subject was withdrawn from the study and followed until the outcome of the pregnancy was known.

Five pregnancies were reported during the development program for minocycline foam, 1.5%. Three subjects were treated with minocycline foam, 1.5%, 1 with vehicle, and 1 with minocycline foam, 4% in a dermal safety study submitted as supportive safety information for this NDA. Pregnancy outcomes in subjects treated with minocycline foam, 1.5%, included 1 healthy baby and 2 for which the outcome is unknown.

Literature Search

The use of tetracycline class drugs orally during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown); retardation of skeletal development on the developing fetus has also been observed in animal studies. The Maternal Health Team completed a review of AMZEEQ (minocycline) topical foam, 4% (NDA 212379) on July 15, 2019. Because the formulation of minocycline foam, 1.5% is identical to AMZEEQ topical foam except for the concentration of the active moiety, information from the review on AMZEEQ topical foam will support labeling recommendations for minocycline foam, 1.5% as well.

Per Dr. Jane Liedtka, the reviewer from the Maternal Health Team of the Division of Pediatric and Maternal Health (DPMH), the Applicant referenced several publications previously reviewed in the 2017 DPMH review for MINOLIRA (minocycline hydrochloride) Extended-Release Tablets. DPMH conducted a search of published literature in PubMed regarding minocycline and its effects on fertility and found no new relevant publications. In her review dated July 15, 2019, Dr. Liedtka provided labeling recommendations for Section 8.1 (Pregnancy) and 8.2 (Lactation) as well as the following comments:

Pregnancy

The following statement will be included in Section 8.1 of labeling for minocycline foam, 1.5%:

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"Available data with ZILXI (minocycline foam, 1.5%) use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Systemic absorption of ZILXI in humans is low following once daily topical administration of ZILXI under maximal clinical use conditions *[see Clinical Pharmacology (12.3)]*. Because of low systemic exposure, it is not expected that maternal use of ZILXI will result in significant fetal exposure to the drug."

Lactation

Minocycline is known to be excreted into human milk at low levels after oral administration. However, because the exposure threshold is not known for the potential adverse effects of minocycline on the infant (tooth discoloration and inhibition of bone growth), the following statement will be included in Section 8.2 of labeling for minocycline foam, 1.5%:

"Tetracycline-class drugs, including minocycline, are present in breast milk following oral administration. It is not known whether minocycline is present in human milk after topical administration to the nursing mother. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with ZILXI *[see Warnings and Precautions (5.2)]*."

Females and Males of Reproductive Potential

Concerns about the interaction between low dose estrogen contraception and effects on male fertility are included in the labeling for oral minocycline. DPMH recommended omitting both of these entries from the labeling for topical use of AMZEEQ topical foam given the very low absorption seen in maximal use studies. DPMH recommends omitting sub-Section 8.3 from labeling for AMZEEQ topical foam. This section will also be omitted from labeling for minocycline foam, 1.5%.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment-Emergent Adverse Events (TEAEs)

In the combined Phase 2/3 safety pool, 418/1678 (24.9%) of subjects reported a TEAE. This included 261/1087 (24.0%) of subjects treated with minocycline foam, 1.5% and 152/591 (25.7%) of subjects treated with vehicle. The most frequently reported TEAEs were in the system-organ class (SOC) of Infections and infestations. In this SOC, the most common preferred terms (PTs) were viral upper respiratory tract infection, upper respiratory tract infection, and nasopharyngitis.

For this topically applied product, application site reactions were of particular interest. Application site reactions reported as AE will be discussed here; results from the active assessment of local safety will be discussed in Section 8.2.5 of this review. In the SOC of General Disorders and Administration Site Conditions, application site erythema, pain and pruritus were reported by ≤0.5% of subjects. There was no imbalance between minocycline foam, 1.5% and vehicle for these TEAEs.

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TEAEs by SOC are presented in order by descending frequency in the table below:

Table 28: TEAE by System Organ Class, Phase 2/3 Safety Population

System Organ Class	Minocycline Foam 1.5% (n=1087)	Vehicle Foam (n=591)
Infections and infestations	112 (10.3%)	74 (12.5%)
Skin and subcutaneous tissue disorders	34 (3.1%)	22 (3.7%)
Gastrointestinal disorders	34 (3.1%)	10 (1.7%)
Nervous system disorders	28 (2.6%)	12 (2.0%)
Musculoskeletal and connective tissue disorders	24 (2.2%)	7 (1.2%)
Injury, poisoning and procedural complications	18 (1.7%)	12 (2.0%)
Respiratory, thoracic and mediastinal disorders	14 (1.3%)	15 (2.5%)
General disorders and administration site conditions	13 (1.2%)	13 (2.2%)
Vascular disorders	13 (1.2%)	5 (0.8%)
Investigations	13 (1.2%)	4 (0.7%)
Metabolism and nutrition disorders	8 (0.7%)	4 (0.7%)
Eye disorders	9 (0.8%)	2 (0.3%)
Surgical and medical procedures	6 (0.6%)	2 (0.3%)
Psychiatric disorders	6 (0.6%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (0.6%)	1 (0.2%)
Cardiac disorders	2 (0.2%)	4 (0.7%)
Immune system disorders	3 (0.3%)	3 (0.5%)
Reproductive system and breast disorders	3 (0.3%)	3 (0.5%)
Blood and lymphatic system disorders	1 (0.1%)	4 (0.7%)
Renal and urinary disorders	3 (0.3%)	2 (0.3%)
Ear and labyrinth disorders	4 (0.4%)	1 (0.2%)
Endocrine disorders	0 (0.0%)	1 (0.2%)
Social circumstances	1 (0.1%)	0 (0.0%)

Abbreviation: TEAE = treatment-emergent adverse event
Source: Reviewer's Table from JReview using FX2015-10, FX2016-11, and FX2016-12 datasets

Treatment-Emergent Adverse Events by Severity

Most TEAEs were mild or moderate in severity. Six (6/1087; 0.6%) subjects treated with minocycline foam, 1.5% experienced 8 severe TEAEs, and 8 (8/591; 1.4%) subjects in the vehicle group experienced 10 severe TEAEs. The only treatment-related severe TEAE was skin burning sensation, which occurred in one subject treated with vehicle foam in Trial FX2015-10. Severe TEAEs that were considered serious are discussed in the previous subsection of this review. Severe TEAEs by SOC and PT are presented in the table below:

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Table 29: Severe TEAE by SOC and PT Phase 2 and 3 NDA 213690

System Organ Class	Preferred Term	Minocycline Foam 1.5% (n=1087)	Vehicle Foam (n=591)
Cardiac disorders	Myocardial infarction	0 (0.0%)	1 (0.2%)
General disorders and administration site conditions	Application site pain	1 (0.1%)	0 (0.0%)
	Pyrexia	0 (0.0%)	1 (0.2%)
Infections and infestations	Gastroenteritis	0 (0.0%)	1 (0.2%)
	Influenza	1 (0.1%)	0 (0.0%)
	Pyelonephritis acute	1 (0.1%)	0 (0.0%)
Injury, poisoning and procedural complications	Fall	0 (0.0%)	1 (0.2%)
	Upper limb fracture	0 (0.0%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	Osteoarthritis	0 (0.0%)	1 (0.2%)
Nervous system disorders	Cerebral hemorrhage	1 (0.1%)	0 (0.0%)
	Hemiparesis	1 (0.1%)	0 (0.0%)
	Post-traumatic headache	1 (0.1%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Asthma	0 (0.0%)	1 (0.2%)
	Dyspnea	0 (0.0%)	1 (0.2%)
	Pulmonary embolism	1 (0.1%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Rosacea	1 (0.1%)	0 (0.0%)
	Skin burning sensation	0 (0.0%)	1 (0.2%)
Surgical and medical procedures	Wisdom teeth removal	0 (0.0%)	1 (0.2%)
	Subjects	6 (0.6%)	8 (1.4%)
	Events	8	10

Abbreviations: PT = MedDRA preferred term; SOC = MedDRA system-organ class; TEAE = treatment-emergent adverse event
Source: Reviewer's Table from JReview using FX2015-10, FX2016-11, and FX2016-12 datasets

TEAEs during Open-Label Extension Study FX2016-13

During the open-label extension Study FX2016-13, the TEAEs and the frequency at which they occurred was similar to the Phase 2/3 safety population. Overall, data from this study was sufficient to demonstrate the long-term safety of minocycline foam, 1.5% for up to 1 year.

Adverse Reactions

The Applicant proposed to include the following information in Section 6.1 (Adverse Reactions/Clinical Trials Experience): "The most common adverse reactions reported during clinical trials were (viral) upper respiratory tract infection, sinusitis, and headache."

The most frequently reported TEAE occurring more frequently in the minocycline foam, 1.5%, are displayed in the Table 30.

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Table 30: Common TEAE Phase 2/3 Safety Population

System Organ Class	Preferred Term	Minocycline Foam 1.5% (n=1087)	Vehicle Foam (n=591)
Infections and infestations	Pooled URI[a]	55 (5.1%)	37 (6.3%)
Nervous system disorders	Headache[b]	15 (1.4%)	10 (1.7%)
Infections and infestations	Sinusitis	12 (1.1%)	3 (0.5%)
Gastrointestinal disorders	Diarrhea	10 (0.9%)	2 (0.3%)

[a] Pooled URI includes preferred terms nasopharyngitis, pharyngitis, rhinitis, upper respiratory tract infection (URTI), and viral URTI
[b] Proposed by Applicant for inclusion in labeling, but reported more frequently in vehicle group
Source: Reviewer's table created in JReview using combined study datasets

In order to better characterize the frequency of upper respiratory infections, we pooled the clinically related PTs of pharyngitis, rhinitis, upper respiratory tract infection (URTI), and viral URTI. After pooling, the frequency is of pooled URTI higher in the vehicle group, which makes a relationship to treatment unlikely. In addition, headache was reported more frequently in the vehicle group as well. Therefore, we do not recommend inclusion of URTI or headache in the Section 6 (Adverse Events) of product labeling.

Although sinusitis occurred in >1% of subjects treated with minocycline foam, 1.5%, the imbalance between active and vehicle groups is small. The imbalance disappears when frequency is rounded to the nearest integer, as is customary for product labeling. We do not recommend inclusion of sinusitis in Section 6 of product labeling.

Although the imbalance between active and vehicle groups for diarrhea is small, after rounding of the frequency to the nearest integer, diarrhea was reported in 1% of subjects treated with minocycline foam, 1.5% and 0% in the vehicle group. None of the TEAE of diarrhea were considered treatment-related by investigators; however, the Applicant did not provide an alternative etiology. In addition, the systemic absorption of minocycline foam, 1.5% is low but measurable, so the biologic plausibility of a relation to treatment cannot be excluded. We recommend inclusion of diarrhea in Section 6 of product labeling.

We propose the following for Section 6 (Adverse Reactions) in product labeling:

The most common adverse reaction reported by ≥1% of subjects treated with ZILXI and more frequently than in subjects treated with vehicle was diarrhea (1% vs. 0%), respectively.

Laboratory Findings

In the Phase 2/3 safety population, the Applicant reported that overall, changes from baseline in the mean, median, and min/max values in serum chemistry and hematology parameters were similar across treatment groups and time points. In addition, the Applicant stated that some shifts from normal at baseline to abnormal at Week 12 (high or low) were observed in most parameters; however, no differences were noted between treatment groups in the incidence rate of the normal to abnormal shifts.

Labeling for SOLODYN includes hepatotoxicity (Section 5.3, Warnings and Precautions) as well as hepatitis and liver failure (Section 6.2, Adverse Reactions, Postmarketing Experience). We

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reviewed TEAE PTs associated with elevated liver enzymes. There was no imbalance between treatment groups for these events. Labeling for SOLODYN also includes metabolic effects (i.e., increase in blood urea nitrogen [BUN]; Section 5.4, Warnings and Precautions). There were no reported TEAEs related to elevated BUN.

In the open-label extension study, the Applicant reports that no notable mean changes were observed in hematology, serum chemistry, or urinalysis parameters during the study. Our review of TEAE PTs related to clinical laboratory abnormalities revealed no clinically meaningful trends.

Vital Signs

In the Phase 2/3 safety population, vital signs (blood pressure and heart rate) were assessed during clinic visits at baseline followed by Weeks 2, 4, 8, and 12. During the open-label extension study, vital signs (blood pressure and heart rate) were assessed during clinic visits at Week 4, then every 6 weeks thereafter. The Applicant reported no clinically significant changes in vital signs.

In the Phase 2/3 safety population, there were 2 TEAE preferred terms related to vital signs. Hypertension was reported in 11 (11/1087; 1.0%) of subjects treated with minocycline foam, 1.5% and 5 (5/591; 0.8%) of subjects in the vehicle group. Tachycardia was reported by 1 (1/591; 0.2%) of subjects in the vehicle group but none in the minocycline foam, 1.5% group.

During the open-label extension study, hypertension was reported in 8 (8/504; 1.6%) of subjects. There was no imbalance in hypertension between the minocycline foam, 1.5% and vehicle groups, and the biologic plausibility of a relationship to treatment is low in this topical drug product.

Electrocardiograms (ECGs)/ QT

The Applicant did not perform ECGs during the Phase 2/3 trials or open-label extension study. In the Summary of Clinical Safety, the Applicant provided a risk assessment of the proarrhythmic potential of minocycline foam, 1.5%. The risk assessment included a review of labeling for the listed drug SOLODYN as well as a literature review of the potentiating effect of minocycline on cardiac signaling.

There are no references to QT/QTc prolongation or cardiac arrhythmia in the labeling for SOLODYN; in addition, the literature review did not reveal evidence of a proarrhythmic potential for minocycline. In addition, the systemic bioavailability of minocycline from topical application for this product is markedly lower compared to the listed drug. This is discussed in more detail in Section 6.2.1 of this review. Based on the above information, treatment with minocycline foam, 1.5% is not anticipated to affect QT intervals or cardiac rhythm.

Immunogenicity

Because the proposed product is not a therapeutic protein, the Applicant did not assess the potential for immunogenicity.

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8.2.5. Analysis of Submission-Specific Safety Issues

Minocycline is an antibiotic in the tetracycline class and is available in oral, IV, and topical formulations. Section 5 (Warnings and Precautions) Labeling for the listed drug, SOLODYN Extended-Release Tablets includes:

Teratogenic Effects
Pseudomembranous Colitis
Hepatotoxicity
Metabolic Effects
Central Nervous System (CNS) Effects
Benign Intracranial Hypertension
Autoimmune Syndromes
Photosensitivity
Serious Skin/Hypersensitivity Reaction
Tissue Hyperpigmentation
Development of Drug-Resistant Bacteria
Superinfection
Laboratory Monitoring

Although systemic exposure following topical administration of minocycline foam, 1.5% was much lower than exposure following oral administration of SOLODYN, we considered the potential for systemic toxicity as well as local safety. Local tolerability, photosensitivity, CNS effects, and serious skin/ hypersensitivity reactions are discussed below.

Local Tolerability

During the Phase 3 trials, the Applicant conducted active assessments of local skin tolerability at each study visit. Telangiectasia, burning/stinging, flushing/blushing, dryness/xerosis, itching, peeling/desquamation, and skin hyperpigmentation were scored on a scale of 0 (“none”), 1 (“mild”), 2 (“moderate”), or 3 (“severe”). Erythema was scored on a scale of 0 (“clear”), 1 (“almost clear”), 2 (“mild”), 3 (“moderate”), or 4 (“severe”). Local tolerability findings at Week 12, based on our analyses, are presented in the table below.

Table 31: Local Safety Assessments, All Levels of Severity at Week 12

	Minocycline Foam 1.5% (n=897)	**Vehicle Foam (n=460)**
Erythema	803 (89.5%)	423 (92.0%)
Telangiectasia	716 (79.8%)	363 (78.9%)
Flushing/Blushing	444 (49.5%)	249 (54.1%)
Dryness/Xerosis	251 (28.0%)	145 (31.5%)
Skin Hyperpigmentation	227 (25.3%)	131 (28.5%)
Itching	209 (23.3%)	110 (23.9%)
Peeling/Desquamation	162 (18.1%)	98 (21.3%)
Burning/Stinging	144 (16.1%)	81 (17.6%)

Source: Reviewer’s Table created in JReview using ISS dataset

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Most of the local tolerability findings were mild or moderate in severity. A total of 8 (0.9%) subjects had severe flushing/blushing, 6 (0.7%) had severe erythema, and one (0.1%) each had severe dryness/xerosis and peeling/desquamation. Investigators characterized the hyperpigmentation as being characteristic of inflammatory and post-inflammatory changes associated with rosacea. The following information regarding local tolerability submitted by the Applicant and agreed upon by the review team will be included in Section 6 (Adverse Reactions):

> During the two Phase 3 trials, local tolerability evaluations were conducted at each study visit by assessment of erythema, telangiectasia, burning/stinging, flushing/blushing, dryness, itching, peeling and hyperpigmentation. Table 1 presents local tolerance assessments by incidence rate (%) and severity grade.
>
> Subjects treated with ZILXI had improved local tolerability signs and symptoms at Week 12 when compared with corresponding baseline values. These occurred at a similar frequency and severity as subjects treated with the vehicle component of ZILXI.

Table 1: Facial Cutaneous Tolerability Assessment

	ZILXI, (%) (N=1008**)		
Symptom/Severity	Mild	Moderate	Severe
Erythema	36.2	18.3	0.7
Telangiectasia	61.0	18.8	0
Burning/Stinging	13.3	2.8	0
Flushing/Blushing	39.0	9.6	0.9
Dryness	23.9	4.0	0.1
Itching	20.0	3.3	0
Skin Peeling	16.1	1.9	0.1
Hyperpigmentation*	22.5	2.8	0

*Hyperpigmentation was most frequently assessed as characteristic of inflammatory and post-inflammatory changes associated with (b) (4) rosacea.
** Of 1008 subjects, 897 had local tolerability assessments at Week 12.

In a 40-week open-label extension safety study of ZILXI (for a total of up to 52 weeks of treatment) [NCT03276936], frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

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Photosensitivity

Labeling for SOLODYN states that "Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported rarely with minocycline. Patients should minimize or avoid exposure to natural or artificial sunlight (e.g., tanning beds or ultraviolet A/B treatment) while using minocycline. If patients need to be outdoors while using minocycline, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician." (Section 5.8, Warnings and Precautions). During the Phase 2 and Phase 3 trials, subjects were advised to avoid prolonged exposure to sunlight. We analyzed AE data from the Phase 2 and Phase 3 trials for PTs associated with photosensitivity. The only PT associated with photosensitivity during these trials was sunburn, which was reported by 2/1087 (0.2%) of subjects treated with minocycline foam, 1.5% and 1/591 (0.2%) of subjects in the vehicle group. During the open-label extension study, sunburn was reported by 2/504 (0.4%) of subjects.

The Applicant also conducted provocative dermal safety studies to evaluate the phototoxicity and photoallergenicity potential of minocycline foam, 4%. These studies were conducted during the development program for minocycline foam, 4% for the treatment of acne vulgaris, and were also submitted as supportive safety information for minocycline foam, 1.5%. Results from these studies are discussed in Section 8.2.8 of this review.

Although we found no safety signal for photosensitivity or phototoxicity in the Phase 3 trials or the provocative dermal safety studies, the systemic exposure threshold for these events has not been characterized. Therefore, we recommend inclusion of Photosensitivity as class labeling in Section 5 (Warnings and Precautions) for minocycline foam, 1.5%.

Central Nervous System (CNS) Effects

Labeling for SOLODYN states that "Central nervous system side effects including light-headedness, dizziness, or vertigo have been reported with minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually rapidly disappear when the drug is discontinued." (Section 5.5, Warnings and Precautions) We analyzed AE data from the Phase 3 trials for PTs associated with CNS effects. During the Phase 2 and Phase 3 trials, the PT vertigo was reported by 2/1087 (0.2%) subjects treated with minocycline foam, 1.5% and no subjects in the vehicle group. In addition, the PT dizziness was reported by 2/1087 (0.2%) subjects treated with minocycline foam, 1.5% and 1/591 (0.2%) subject in the vehicle group. Syncope was reported by 1/1087 (0.1%) subject treated with minocycline foam, 1.5% and no subjects in the vehicle group. During the open-label extension study, these events were reported as follows: vertigo in 5/504 (1.0%), dizziness in 1/504 (0.2%), and syncope in 2/504 (0.4%).

Although we found no safety signal for CNS events, the systemic exposure threshold for these events has not been characterized. Therefore, we recommend inclusion of Central Nervous System Effects as class labeling in Section 5 (Warnings and Precautions) for minocycline foam, 1.5%.

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Hypersensitivity Reactions

Labeling for SOLODYN states that "Cases of anaphylaxis, serious skin reactions (e.g., Stevens-Johnson syndrome), erythema multiforme, and drug rash with eosinophilia and systemic symptoms syndrome have been reported postmarketing with minocycline use in patients with acne..." No such reactions occurred during the Phase 2 and Phase 3 trials. No AE PTs were discovered related to hypersensitivity during the Phase 2 and Phase 3 trials. During the open-label extension study, urticaria was reported by 1/504 (0.2%) subject. Investigators considered the AE of urticaria as unlikely related to treatment.

Although we found no safety signal for serious skin/hypersensitivity reactions, the systemic exposure threshold for these events has not been characterized. Therefore, we recommend inclusion of Serious Skin/Hypersensitivity Reactions as class labeling in Section 5 (Warnings and Precautions) for minocycline foam, 1.5%.

Conclusion

During the development program for minocycline foam, 1.5% we looked for safety signals related to the events described in Section 5 (Warnings and Precautions) of labeling for the listed drug, SOLODYN. Although we found no safety signals for these events, the systemic exposure threshold for these events has not been characterized. Therefore, we recommend all adverse events listed in Section 5 (Warning and Precautions) for SOLODYN to be included in labeling for minocycline foam, 1.5%.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The Phase 3 and open-label extension study protocols included the Subject Satisfaction Questionnaire, which is a patient-reported outcome (PRO). No primary or secondary endpoints were based on this PRO, and it was not included in the multiplicity testing strategy or proposed product labeling. Therefore, data and endpoints based on this PRO are considered exploratory and will not be included in this review.

8.2.7. Safety Analyses by Demographic Subgroups

We conducted additional analyses to evaluate the safety profile of minocycline foam, 1.5% in different demographic subgroups. Because the trials were not powered for these analyses, the data must be interpreted with caution. In the Phase 2/3 safety population, a total of 96.5% of subjects were of white race. No other racial group exceeded 1.1% of the total number of subjects, which precludes meaningful subgroup safety analyses based on race.

For the adverse reaction of diarrhea, there was no clinically meaningful difference in frequency between male and female subjects or subjects age ≥65 years and <65 years. These results are presented in the tables below:

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Table 32: Adverse Reactions by Sex Phase 2/3 Safety Population

	Minocycline Foam 1.5% (n=1087)		Vehicle (n=591)	
Adverse Reaction	**Male (n=315)**	**Female (n=772)**	**Male (n=196)**	**Female (n=395)**
Diarrhea	1 (0.3%)	9 (1.2%)	1 (0.5%)	1 (0.3%)

Denominator is total subjects of same gender/treatment group
Source: Reviewer's Table from JReview using FX2015-10, FX2016-11, and FX2016-12 datasets

Table 33: Adverse Reactions by Age Group Phase 2/3 Safety Population

	Minocycline Foam 1.5% (n=1087)		Vehicle (n=591)	
Adverse Reaction	**Age 18-64 (n=915)**	**Age ≥65 (n=172)**	**Age 18-64 (n=485)**	**Age ≥65 (n=106)**
Diarrhea	8 (0.9%)	2 (1.2%)	1 (0.2%)	1 (0.9%)

Denominator is total subjects of same age/treatment group
Source: Reviewer's Table from JReview using FX2015-10, FX2016-11, and FX2016-12 datasets

Local tolerability findings at Week 12 occurred at similar frequencies across age groups, except for telangiectasia. In subjects treated with minocycline foam, 1.5%, telangiectasia occurred in 142/222 (65.3%) subjects age 18-40 years compared to 446/530 (84.2%) of subjects age 41-64 years and 125/145 (86.2%) of subjects age 65 years or older. The results were similar in the vehicle group. Local tolerability assessment findings at Week 12 were similar between male and female subjects for both minocycline foam, 1.5% and vehicle.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant submitted supportive safety data from a pharmacokinetic (PK) study conducted under conditions of maximal use with the to-be-marketed formulation of minocycline foam, 1.5%. The Applicant also submitted supportive safety data from studies conducted with minocycline foam, 4%, which is approved for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older (AMZEEQ™ [minocycline] topical foam, 4%; NDA 212379]. Other than the concentration of the active moiety, the formulations of the two product are identical. Studies of minocycline foam, 4% submitted in support of this NDA include a PK study conducted under conditions of maximal use, and four provocative dermal safety studies. Safety results from these studies will be summarized briefly below.

Maximal Use PK Studies

<u>Study FX2017-14</u>

This Phase 1 trial was a single-center, nonrandomized, open-label, single-period, PK and safety study under conditions of maximal use. Subjects applied approximately 2 grams of minocycline foam, 1.5% once daily to the entire face. The study population included 20 adult subjects with moderate-to-severe facial papulopustular rosacea defined as IGA score 3 or 4.

Refer to Section 6.2.1 for further details regarding the study design and PK results. The evaluation of safety included:

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- AE/SAE
- Clinical laboratory evaluation (hematology, chemistry, urinalysis)
- ECG
- Pregnancy testing
- Vital signs
- Physical examination

There were no deaths or serious TEAEs, no severe TEAEs, and no TEAEs that resulted in withdrawal of study drug or dose reduction during the study. One subject (1/20; 5.0%) reported a total of 2 TEAEs (arthralgia and headache). The investigator considered the TEAE of arthralgia to be moderate in severity and not related to study drug. The investigator considered the TEAE of headache to be mild in severity and possibly related to study drug.

Study FX2014-03 (Refer to Multi-Disciplinary Review and Evaluation of NDA 212379, Section 8.2.8)

This Phase 1 trial was a single-center, nonrandomized, open-label, active-controlled, 2-period, 2-treatment crossover evaluation of multiple dose topical administration of minocycline foam, 4% compared to oral administration of the LD, SOLODYN Extended-Release Tablets. The maximal use dose of minocycline foam, 4% was 4 grams, which was based on the mean dose of 0.5 grams from the Phase 2 trial. The study population included 30 subjects age 18 years to 35 years with moderate to severe acne vulgaris.

Refer to Section 6.2.1 for further details regarding the study design and PK results. The evaluation of safety included:

- AE/SAE
- Clinical laboratory evaluation (hematology, chemistry, urinalysis)
- Electrocardiogram (ECG)
- Pregnancy testing
- Vital signs
- Physical examination

Safety Results

No deaths, SAEs, or severe TEAEs were reported; no subjects discontinued because of an AE. Two subjects (2/30; 6.7%) reported a total of two TEAEs in the SOLODYN group, and nine subjects (30%) reported a total of 14 TEAEs in the minocycline foam, 4% group. TEAEs are presented in Table 34 below.

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Table 34: Summary of TEAEs by Preferred Term in Trial FX2014-03

	Solodyn (N=30)	FMX-101 (N=30)	Overall (N=30)
Subjects with Any TEAE, n (%)	2 (6.7)	9 (30.0)	11 (36.7)
Dysmenorrhea	0	2 (6.7)	2 (6.7)
Nasal congestion	0	2 (6.7)	2 (6.7)
Rhinorrhea	0	2 (6.7)	2 (6.7)
Asthma	0	1 (3.3)	1 (3.3)
Bronchitis	0	1 (3.3)	1 (3.3)
Cough	1 (3.3)	0	1 (3.3)
Dermatitis Contact	0	1 (3.3)	1 (3.3)
Headache	1 (3.3)	0	1 (3.3)
Oropharyngeal Pain	0	1 (3.3)	1 (3.3)
Pharyngitis Streptococcal	0	1 (3.3)	1 (3.3)
Respiratory Tract Congestion	0	1 (3.3)	1 (3.3)
Tonsillitis	0	1 (3.3)	1 (3.3)

Note: Counts reflect numbers of subjects who reported 1 or more AEs that mapped to the MedDRA preferred term. TEAEs were defined as AEs with an onset of date on or after the date of the first dose of study medication. TEAEs were assigned to the last treatment the subject had received on or before onset date.
Abbreviations: AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Source: FX2014-03 CSR, Table 12-2, p,.48

All TEAEs were mild or moderate in severity and investigators considered none to be related to treatment. There were no clinically significant abnormalities in vital signs, physical examination, ECGs, or safety laboratory results in any subject. Investigators did not conduct an active assessment of local tolerability during this study.

Dermal Safety Studies

The Applicant conducted four Phase 1 provocative dermal safety studies in healthy adult subjects with the to-be-marketed formulation of minocycline topical foam, 4% (NDA 212379). The trials evaluated the potential of minocycline foam, 4% for sensitization, irritation, phototoxicity, and photoallergenicity. The dermal safety studies revealed no evidence of contact sensitization, cumulative irritation, phototoxicity, or photoallergenicity. For further details regarding the dermal safety studies, refer to Multidisciplinary Review and Evaluation of NDA 212379, Section 8.2.8.

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8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct a specific clinical trial to evaluate human carcinogenicity or tumor development. During the development program, the trial designs did not include specific assessments to evaluate for carcinogenicity or screen for safety signals related to malignancy. During the Phase 3 trials, basal cell carcinoma was reported in 1 subject treated with minocycline foam, 1.5% and one subject in the vehicle group. In addition, one subject in the minocycline foam, 1.5% group had squamous cell carcinoma of skin. In the open-label extension study, the following malignancies were reported (each occurred in one subject unless otherwise noted: basal cell carcinoma (3 subjects), malignant melanoma, neoplasm skin, prostate cancer (2 subjects), and squamous cell carcinoma. Investigators considered none of the events of malignancy to be related to treatment with minocycline foam, 1.5%.

The Applicant submitted a 505(b)(2) application, using SOLODYN (minocycline hydrochloride) Extended-Release Tablets as the listed drug. The Applicant intends to rely on nonclinical information from the approved label for the listed drug, including carcinogenicity. A waiver request for conduct of a nonclinical dermal carcinogenicity study with minocycline foam, 4% was granted based on the results from a 39-week dermal toxicity study with minocycline foam in minipigs. No preneoplastic or hyperplastic changes were reported in the skin in the 39-week dermal toxicology study in minipigs. Per the nonclinical toxicology reviewer, “this waiver is applicable to (minocycline foam, 1.5%) because (it) has the identical formulation except that the concentration of minocycline is 2.7-fold lower with a compensatory increase in the amount of light mineral oil.” Refer to Section 5.5.3 of this review for further information regarding the nonclinical evaluation for carcinogenicity.

Human Reproduction and Pregnancy

This was discussed in Section 8.2.4 Safety Results in the Significant Adverse Events subsection.

Pediatrics and Assessment of Effects on Growth

As a new dosage form, minocycline foam, 1.5% triggers the requirement under the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c) for an assessment of safety and effectiveness of the product for inflammatory lesions of (b) (4) rosacea in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Applicant has requested a full waiver of the requirement to conduct studies in pediatric subjects because studies would be impossible or highly impracticable. The Agency agreed and will not require postmarketing assessments under the Pediatric Research Equity Act.

Refer to Section 10 of this review for further details regarding the Agreed Initial Pediatric Study Plan.

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Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

Per the Applicant, no overdoses occurred in the minocycline foam, 1.5% clinical program for inflammatory lesions of rosacea. There is no information available on overdose with minocycline foam, 1.5%.

Drug Abuse Potential/ Withdrawal and Rebound

The Applicant did not evaluate abuse potential and did not design or conduct trials to evaluate subjects for withdrawal or rebound. However, based on the mechanism of action and low systemic exposure, there is no reason to anticipate any potential for abuse or dependency. Therefore, Section 10 will be omitted form product labeling.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Minocycline foam, 1.5% is not marketed in any jurisdiction. There are no ongoing nonclinical or clinical trials that could provide additional data to inform the current or anticipated safety evaluation for this product. Therefore, no postmarketing safety data are available.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the safety data for minocycline foam, 1.5% identified no safety signals. There are no safety concerns that are expected to change the favorable risk/benefit assessment or lead to increased risk with administration of minocycline foam, 1.5% in the postmarket setting.

8.2.11. Integrated Assessment of Safety

The safety profile for minocycline foam, 1.5% was adequately characterized during the drug development program. The primary safety database consisted of 1678 subjects from Phase 2 trial FX2015-10 and Phase 3 trials FX2016-11 and FX2016-12 (the Phase 2/3 safety population). The Phase 2/3 safety population includes all randomized subjects who received at least one dose of the study medication during double-blind treatment in the Phase 2 and Phase 3 trials. Safety data from this population was analyzed according to the treatment that subjects received.

Based on review of the safety data, no serious ARs were identified and therefore Section 4 (Contraindications) in product labeling will include only hypersensitivity to any of the tetracyclines or any of the ingredients within minocycline foam, 1.5%. Although systemic exposure from topical administration of minocycline foam, 1.5% was much lower than exposure from SOLODYN administered orally, the exposure threshold for the events listed in Section 5 (Warnings and Precautions) of labeling for SOLODYN is not definitively known. Therefore, all of

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the Warnings and Precautions in the labeling for SOLODYN will be included as class labeling in labeling for minocycline foam, 1.5%.

Treatment with minocycline foam, 1.5% was not associated with an increased risk of mortality or SAEs. Two deaths occurred during the development program; neither were related to treatment with minocycline foam, 1.5%. In the Phase 2/3 safety population, SAEs occurred in 0.5% of subjects treated with minocycline foam, 1.5% and 1.0% of subjects treated with vehicle. Among subjects in the minocycline foam, 1.5% group, SAEs included nausea, chest discomfort, fatigue, seasonal allergy, contusion, dehydration, cerebral hemorrhage, hemiparesis, syncope, dyspnea, pulmonary embolism, and hypertension. In the vehicle group, SAEs included myocardial infarction, tachycardia, gastrointestinal hemorrhage, chest pain (2 events in 1 subject), pyrexia, gastroenteritis, asthma, dyspnea, and hypertension. During the open-label extension Study FX2016-13, a total of 13 (2.6%) subjects overall experienced 15 SAEs which included pneumonia, malignant melanoma, subdural hematoma, cerebrospinal fluid leakage, syncope, death, periorbital cellulitis, staphylococcal infection, labyrinthitis, cerebrovascular accident, hypokalemia, post-procedural hemorrhage, large intestinal obstruction, chronic obstructive pulmonary disease and appendicitis perforated. There were no SAEs considered related to treatment with minocycline foam, 1.5% or vehicle.

The most common AR was diarrhea, which was reported in 1% of subjects treated with minocycline foam, 1.5% and 0% of subjects treated with vehicle. The Applicant also conducted active assessments of local tolerability, the results of which were as follows in subjects treated with minocycline foam, 1.5% at Week 12 (all levels of severity combined): erythema (89.5%), telangiectasia (79.8%), flushing/blushing (49.5%), dryness/xerosis (28.0%), skin hyperpigmentation (25.3%), itching (23.3%), peeling/desquamation (18.1%), and burning/stinging (16.1%). Local tolerability findings occurred with a similar frequency and severity in the vehicle group. Most of the local tolerability findings were mild or moderate in severity. Investigators characterized the hyperpigmentation as being characteristic of inflammatory and post-inflammatory changes associated with rosacea.

Although the Applicant did not define pregnancy as an AE, subjects who became pregnant were withdrawn from the study and followed until the outcome of the pregnancy was known. Five pregnancies were reported during the development program for minocycline foam, 1.5%. Three subjects were treated with minocycline foam, 1.5%, 1 with vehicle, and 1 with minocycline foam, 4% in a dermal safety study submitted as supportive safety information for this NDA. Pregnancy outcomes in subjects treated with minocycline foam, 1.5%, included 1 healthy baby and 2 for which the outcome is unknown. In a review dated July 15, 2019 for minocycline foam, 4% (NDA 212379), Jane Liedtka, MD, the reviewer from the DPMH, concluded that due to “minimal” systemic exposure, it is not expected that maternal use of minocycline foam, 4% will result in significant fetal exposure to the drug. This also applies to minocycline foam, 1.5%. Section 8.1 (Pregnancy) of product labeling will convey that the available data with use of minocycline foam, 1.5% are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

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The currently available data from one Phase 2 and two Phase 3 trials with a treatment period of 12 weeks demonstrate that minocycline foam, 1.5% appears safe for the treatment of inflammatory lesions of rosacea in adults. The Applicant also submitted long-term safety data from an additional 40 weeks of treatment in an open-label extension study. The safety profile for long-term use (up to 52 weeks) of minocycline foam, 1.5% appears similar to that for short-term use. Postmarketing risk management will include professional labeling and routine pharmacovigilance. As the moiety is well characterized, the review team recommends no other risk management tools and assessments (REMS or clinical postmarketing studies).

8.3. Summary and Conclusions

8.3.1. Statistical Issues

The center by treatment interaction was statistically significant at the 0.1 level for the inflammatory lesion count endpoint at Week 12 in Study FX2016-12. Efficacy by center was further explored through plots and descriptive statistics, as presented in Figure 12 through Figure 15. The statistical reviewer conducted a sensitivity analysis where centers were removed one-by-one from the analysis to investigate their impact on the overall results. The results showed that no single center drove the overall efficacy results. The large number of centers and small number of subjects per treatment arm in most centers likely describes the large variation. The centers with higher numbers of subjects per treatment arm tended to have more consistent treatment effects with the observed overall treatment effect.

Comparing the efficacy results for the Phase 2 Trial FX2015-10 and the Phase 3 Trials FX2016-11/12, the mean change from baseline in inflammatory lesion count was about two times lower for the vehicle arm in Phase 2 Trial FX2015-10 compared to the vehicle arm in the Phase 3 trials. However, the Phase 2 Trial FX2015-10 enrolled subjects with a wider range of inflammatory lesion count (~12-189 lesions) compared to the Phase 3 trials (~15-75 lesions). The statistical reviewer conducted sensitivity analysis to explore the change in inflammatory lesion count in Trial FX2015-10 for the subgroup of subjects with baseline number of inflammatory lesions between 15-75 in comparison with the same results in the Phase 3 trials. The treatment effect remained higher in Trial FX2015-10 compared to the Phase 3 trials. Differences in the population between the Phase 2 trial (FX2015-10) and the Phase 3 trials (FX2016-11/12) could have contributed to the higher treatment effect in the inflammatory lesion count. The Phase 2 trial was conducted in Germany, while the Phase 3 trials were conducted in the US. The Phase 3 trials enrolled subjects with “no more than 2 nodules on the face”, while there was no such enrollment criterion for the Phase 2 trial. The Phase 3 trials enrolled a slightly higher proportion of females (~70%) subjects compared to the Phase 2 trial (~60%).

8.3.2. Conclusions and Recommendations

To establish the effectiveness of minocycline foam, 1.5%, the Applicant submitted data from two identical Phase 3, multicenter, randomized, double-blind, vehicle controlled, 2-arm safety

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and efficacy trials conducted in subjects ≥18 years of age with moderate to severe papulopustular rosacea, defined as:

- 15-75 facial papules and pustules
- ≤2 nodules
- IGA score 3 (“moderate”) or 4 (“severe”)
- History erythema or flushing of face.

Subjects were randomized 2:1 to treatment with minocycline foam, 1.5% or vehicle foam. Both trials included a double-blind treatment period of 12 weeks during which subjects applied minocycline foam, 1.5% or vehicle foam to the entire face once daily. The coprimary endpoints for the Phase 3 trials were:

- Absolute change from baseline in the inflammatory lesion count at Week 12 AND
- Treatment success at Week 12 defined as an IGA score of 0 or 1, and at least a two-grade improvement (decrease) from baseline at Week 12

Minocycline foam, 1.5% was statistically superior to vehicle (p values ≤0.0218) on the coprimary endpoints in both Phase 3 trials. Although the protocols stated that secondary endpoints would be tested sequentially if the coprimary endpoints were significant, the SAPs and Clinical Study Reports state that no adjustments were made for multiple comparisons of endpoints. Therefore, statistical significance cannot be determined, and p-values are not presented for secondary endpoints; this data will not be included in product labeling. Refer to Section 8.1.1.4 for discussion of the coprimary endpoints and 8.1.1.6 for discussion of the secondary endpoints.

The Applicant conducted a comprehensive assessment of safety of minocycline foam, 1.5% in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions.

Submitted safety and efficacy data support approval of NDA 213690, ZILXI (minocycline) topical foam, 1.5% for the topical treatment of inflammatory lesions (b) (4) of rosacea in patients 18 years of age and older.

9. Advisory Committee Meeting and Other External Consultations

The Agency conducted no Advisory Committee Meeting regarding this application because the safety profile of the moiety is well characterized.

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10. Pediatrics

The Applicant has established the safety and efficacy of minocycline foam, 1.5% for the treatment of inflammatory lesions (b) (4) of rosacea in adults. The adult population is the relevant population for the indication for which the Applicant seeks approval. Rosacea is reported to be rare in children.[1,2]

Because this product has a new dosage form, it triggers the requirement under the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c) for an assessment of safety and effectiveness of the product for the treatment of inflammatory lesions (b) (4) of rosacea in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Applicant submitted an initial Pediatric Study Plan (iPSP) on July 19, 2019 wherein they requested that the Agency waive the requirement for a pediatric assessment for all pediatric age groups. The Applicant stated that necessary studies would be impossible or highly impractical because there are too few children with (b) (4) rosacea (section 505B(a)(4)(A)(iii) of the Act). The Agency agreed with the Applicant and sent a written response on August 29, 2019. The Applicant submitted an Agreed iPSP on September 12, 2019. At the meeting of October 1, 2019, the Pediatric Review Committee concurred with the recommendation from the Division. The Agreed iPSP Letter was sent on October 8, 2019. Therefore, postmarketing assessments under the Pediatric Research Equity Act are not required.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton/container labels for minocycline foam, 1.5%. The review team provided recommendations regarding PI which are provided throughout this review. Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed PI, PPI, IFU, container labels, and carton labeling. DMEPA concluded that the PI, PPI, and IFU for ZILXI (minocycline) topical foam, 1.5% were acceptable from a medication error perspective. DMEPA also stated that the container labels and carton labeling can be improved to increase the prominence of important information and to facilitate product identification (Refer to review dated 1/31/2020). The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI, and carton/container labeling. Refer to the OPDP review by Laurie Buonaccorsi, PharmD, dated March 17, 2020. These comments are reflected in final labeling. Table 35 provides the location of the labeling discussion in this review for each section of product labeling.

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Table 35: Location of the Labeling Discussion for Significant High-Level Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Section 1.1
2 DOSAGE AND ADMINISTRATION	Section 6.2.2
4 CONTRAINDICATIONS	Section 8.2.11
5 WARNINGS AND PRECAUTIONS	Sections 8.2.5, 8.2.11
6 ADVERSE REACTIONS	Section 8.2.4, 8.2.5
7 DRUG INTERACTIONS	Section 6.3.2
8 USE IN SPECIFIC POPULATIONS	Sections 5.5, 8.2, 10, 19.3
12 CLINICAL PHARMACOLOGY	Section 6
14 CLINICAL STUDIES	Section 8.1
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling: Sections 4, 5, 6, and 15

11.2. Patient Labeling

The Division of Medical Policy Programs and OPDP reviewed and provided comments regarding the PPI and IFU for minocycline foam, 1.5%. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Susan Redwood, MPH, BSN, RN and Laurie Buonaccorsi, PharmD dated 3/18/2020.

12. Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and standard postmarketing surveillance are not warranted at this time.

13. Postmarketing Requirements and Commitment

None.

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14. Appendices

14.1. References

The references are included as footnotes.

14.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for minocycline topical foam. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were Trials FX2016-11, and FX2016-12 which provided the primary data to establish effectiveness and safety of this product. Refer to Section 8.1.1 for the trial designs.

Covered Clinical Study (Name and/or Number): FX2016-11

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 54		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not Applicable (N/A) Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

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Covered Clinical Study (Name and/or Number): FX2016-12

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 47		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not Applicable (N/A) Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

14.3.1. Multiple of Human Exposure Calculations

The applicant calculated the multiples of human exposure in the ZILXI label using the multiple of human exposure provided in the SOLODYN label (the listed drug), the geometric mean AUC from the SOLODYN arm of the comparative bioavailability study (15060 or 15100 ng*hr/mL), and the geometric mean AUC for subjects treated with ZILXI under maximal use conditions on Day 1 (17.9 ng*hr/mL).

The multiples of human exposure in the ZILXI label were recalculated using the multiple of human exposure provided in the SOLODYN label (the listed drug), mean human AUC from the SOLODYN arm of the comparative bioavailability study (15475 ng*hr/mL) and the mean AUC value for subjects treated with ZILXI under maximal use conditions on Day 1 (22.5 ng*hr/mL).

For example, the calculation for the multiple to be used for the rat embryofetal development study in labeling is provided below.

Proposed multiple: (b) (4)

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The multiples of human exposure to be used in the ZILXI label are provided below. No multiples of human exposure are provided for the carcinogenicity studies contained in the SOLODYN label. Therefore, no multiples of human exposure will be provided for the carcinogenicity studies contained in the ZILXI label.

Table 36: Multiples of Human Exposure Based on AUC Comparison[e]

Study	Route	LOAEL[a]/NOAEL[b] (mg/kg/day)	Multiples of Human Exposure (SOLODYN)[c]	Multiples of Human Exposure (Minocycline Foam, 1.5%)
Carcinogenicity study in rats	Oral	200[a]	N/A[d]	-
Carcinogenicity study in mice	Oral	150[b]	N/A[d]	-
Embryofetal development study in rats	Oral	30[a]	~3	2,063 (2,000)
Embryofetal development study in rats	Oral	10[a]	~1	688 (680)
Embryofetal development study in rabbits	Oral	100 [a]	~2	1,376 (1,300)
Pre- and postnatal development study in rats	Oral	50 [a]	~2.5	1,719 (1,700)
Fertility and early embryonic development in rats	Oral	300[a]	~40	27,512 (27,500)
Fertility and early embryonic development in rats	Oral	100[a]	~15	10,317 (10,000)

[a,b] The LOAEL or NOAEL values provided in SOLODYN label.
[c] The multiples of human exposure (i.e., AUC in animal study/33320 ng*hr/mL) provided in SOLODYN label.
[d] Not available in SOLODYN label.
[e] Using the human mean AUC value of 15475 ng*hr/mL from the SOLODYN arm of the comparative bioavailability study and 22.5 ng*hr/mL in subjects treated with minocycline foam, 1.5% under maximal clinical use conditions
Abbreviations: LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; AUC = area under the concentration time curve

14.3.2. Labeling

Recommended revision to the nonclinical portions of labeling

Revisions to the Applicant's proposed wording for the nonclinical and related sections of the label are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the ZILXI label text.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ZILXI is a tetracycline-class drug indicated to treat (b) (4) inflammatory lesions (b) (4) (b) (4) of rosacea in adults.

8.1 Pregnancy

Risk Summary

Available data with ZILXI use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Systemic absorption of ZILXI in humans is low following once daily topical administration of ZILXI under maximal clinical use conditions *[see Clinical Pharmacology (12.3)]*. Because of low systemic exposure, it is not expected that maternal use of ZILXI will result in significant fetal exposure to the drug.

Tetracycline-class drugs may cause permanent discoloration of teeth and reversible inhibition of bone growth when administered orally during pregnancy *[see Warnings and Precautions 5.2, 5.3, 5.4)* (b) (4)

Animal reproduction studies were not conducted with ZILXI. In animal reproduction studies, oral (b) (4) administration of minocycline (b) (4) to pregnant rats and rabbits during organogenesis induced skeletal malformations in fetuses at systemic exposures of 2 (b) (4) 00 and 1 (b) (4) 300 times, respectively, the maximum recommended human dose (MRHD; based on AUC comparison) of ZILXI (*see Data*).

Data

Animal Data

Results of animal studies with oral administration indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus (b) (4)

Minocycline induced skeletal malformations (bent limb bones) in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (2, (b) (4) 00 times and 1 (b) (4) 00 times, respectively, the systemic exposure at the MRHD based on AUC comparison). Reduced mean fetal body weight was observed when minocycline was orally administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (680 (b) (4) times the systemic exposure at the MRHD based on AUC comparison).

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Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day ([(b) (4)] 1,700 times the systemic exposure at the MRHD based on AUC comparison). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

12.1 Mechanism of Action

The mechanism of action of ZILXI for the treatment of [(b) (4)] inflammatory lesions of rosacea is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female rats once daily for up to 104 weeks at dosages up to 200 mg/kg/day, minocycline hydrochloride was associated in both [(b) (4)] sexes with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female mice once daily for up to 104 weeks at dosages up to 150 mg/kg/day, exposure to minocycline hydrochloride did not result in a significantly increased incidence of neoplasms in either males or females.

Minocycline was not mutagenic in vitro in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.

Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day ([(b) (4)] 27,500 times the [(b) (4)] systemic exposure at the MRHD based on AUC comparison). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats ([(b) (4)] 10,000 or 27,500 times, respectively, the [(b) (4)]

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systemic exposure at the MRHD based on AUC comparison), adversely affected spermatogenesis.

Effects observed at 300 mg/kg/day of oral minocycline included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

14.4. OCP Appendices (technical documents supporting OCP recommendations)

14.4.1. Individual Study Review

14.4.1.1. Study FX2014-03

Title: A Phase 1 study to characterize minocycline bioavailability following multiple dose topical administration of FMX-101 compared to oral administration of Solodyn (minocycline hydrochloride) extended release tablets

See detailed clinical pharmacology review in Section 19.4.1.1 Study FX2014-03 in NDA 212379 Multi-Disciplinary Review and Evaluation dated 10/18/2019 in DARRTS.

19.4.1.2 Study FX2017-14

Title: A Phase 1 study to characterize minocycline pharmacokinetics (PK) in subjects with facial papulopustular rosacea following multiple-dose topical administration of FMX103 under maximum use conditions.

Objectives: To characterize minocycline PK following multiple-dose administration of FMX103 1.5% minocycline foam in subjects with moderate-to-severe facial papulopustular rosacea.

Methods: Twenty subjects with PPR received topical QD application of approximately 2 gm of FMX103 1.5% minocycline foam (FMX103) to the entire face for 14 days. The amount and time of each application of FMX103 was recorded.

PK assessment: Blood samples were collected on Days 1 and 14 (Predose and 2, 4, 8, 12, 16, and 24 hours post-dose). Predose blood samples were collected on Days 6, 9, 11, and 12. Additional blood samples were collected on Days 16, 17, and 18.

Results: All 20 subjects completed the study: 14 subjects (70%) were female and all subjects were white. All subjects had measurable plasma concentrations of minocycline, except one subject ([redacted] (b) (6)), for whom all plasma concentrations were below the limit of quantification, the reason for which was not determined. The lower limit of quantification was 0.257 ng/mL.

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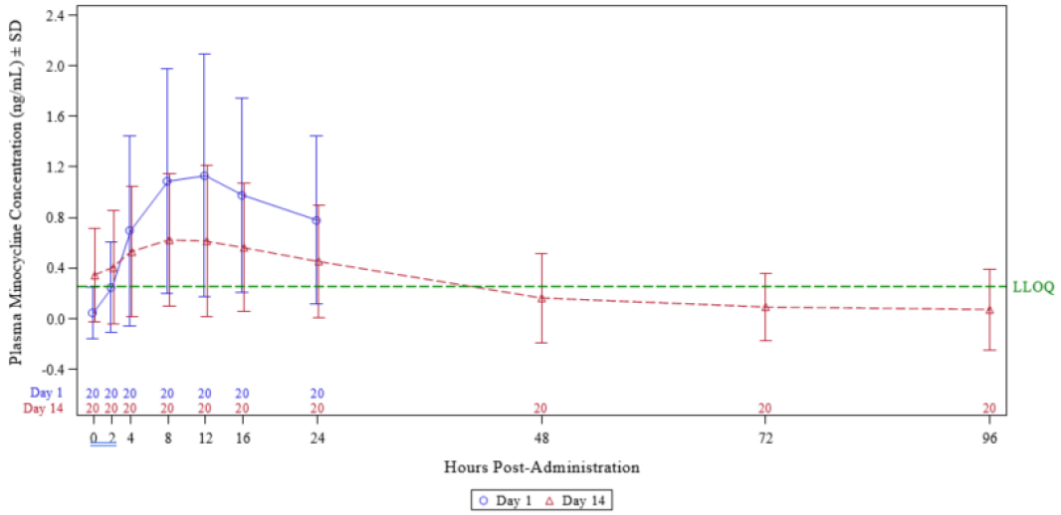
The study demonstrated that plasma concentrations of minocycline over time were low following multiple topical application over 14 days (Figure 16 and Table 37). Mean ± SD trough concentrations of plasma minocycline following Days 1 and 14 treatments were 0.78±0.66 ng/mL and 0.45±0.44 ng/mL, respectively, indicating that steady-state was reached within a day (Table 37). The systemic exposure on Day 14 was numerically lower than Day 1 and this could be due to resolution of the disease. Mean ± SD of C_{max} of plasma minocycline on Days 1 and 14 were 1.3±0.92 ng/mL and 0.75±0.54 ng/mL, respectively (Table 38). Mean ± SD of $AUC_{0\text{-}tau}$ of plasma minocycline on Days 1 and 14 were 22.5±16.2 h·ng/mL and 15.8±11.4 h·ng/mL, respectively (Table 38). Drug accumulation was not evident over the 14-day treatment period as accumulation ratio was 0.77 (Table 38).

Figure 16: Plasma Concentrations of Minocycline on Days 1 and 14 Following Topical Application of FMX103



LLOQ = lower limit of quantification
Note: Day 1 plasma concentrations were only collected up to 24 hours post-administration.
Note: The LLOQ for plasma minocycline concentration is 0.257 ng/mL. Any below the limit of quantification (BLQ) values were set to zero.
Source: 1 in 2.7.2 Summary of clinical pharmacology studies

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Table 37: Plasma Concentrations of Minocycline of Days 1 and 14 in Subjects With PPR Treated With FMX103

Time of Sample[1]	Mean (SD) Concentrations of Minocycline in Plasma (ng/mL) All Subjects (N=20)	
	Day 1	Day 14
Predose	0.045 (0.203)	0.342 (0.370)
2 hours	0.245 (0.356)	0.403 (0.447)
4 hours	0.696 (0.752)	0.528 (0.515)
8 hours	1.09 (0.887)	0.622 (0.526)
12 hours	1.13 (0.960)	0.613 (0.598)
16 hours	0.975 (0.771)	0.562 (0.506)
24 hours	0.777 (0.664)	0.453 (0.442)
48 hours	NA	0.163 (0.352)
72 hours	NA	0.092 (0.266)
96 hours	NA	0.072 (0.320)

BLQ = below the limit of quantification; NA = not applicable
[1] The samples collected 24 hours, 48 hours, 72 hours, and 96 hours relative to the Day 14 dose application were collected on Days 15, 16, 17, and 18, respectively.
Note: Descriptive statistics of plasma minocycline concentrations include data from Subject (b) (6), for whom all plasma concentrations were BLQ. For summaries of plasma concentrations, BLQ values were set to zero.
Source: 6 in 2.7.2 Summary of clinical pharmacology studies

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Table 38: Summary of PK Parameters of Minocycline in Subjects With PPR Treated With FMX103

		All Subjects (N=19)	
PK Parameter	**Statistic**	**Day 1**	**Day 14**
C_{max} (ng/mL)	n	19	19
	Mean (SD)	1.30 (0.916)	0.745 (0.543)
	CV (%)	70.3	72.8
	Geometric Mean[1]	1.05	0.614
	Median	0.915	0.526
	Minimum, Maximum	0.346, 3.41	0.285, 2.04
T_{max} (h)	n	19	19
	Mean (SD)	11.8 (4.07)	9.5 (3.82)
	CV (%)	34.5	40.3
	Median	12.0	8.0
	Minimum, Maximum	8, 24	4, 16
$AUC_{0\text{-}tldc}$ (ng*h/mL)	n	19	19
	Mean (SD)	21.3 (16.2)	23.1 (34.1)
	CV (%)	76.1	147.3
	Geometric Mean[1]	16.2	11.2
	Median	14.8	9.93
	Minimum, Maximum	3.26, 59.3	0.285, 142
C_{24} (ng/mL)	n	18	16
	Mean (SD)	0.863 (0.643)	0.566 (0.424)
	CV (%)	74.5	74.8
	Geometric Mean[1]	0.709	0.476
	Median	0.639	0.388
	Minimum, Maximum	0.298, 2.68	0.276, 1.68
$AUC_{0\text{-}tau}$ (ng*h/mL)	n	18	16
	Mean (SD)	22.5 (16.2)	15.8 (11.4)
	CV (%)	72.0	72.0
	Geometric Mean[1]	17.9	13.2
	Median	15.3	10.8
	Minimum, Maximum	7.36, 59.9	6.95, 43.6
R_{ACC}	n	NA	15
	Mean (SD)	NA	0.772 (0.342)
	CV (%)	NA	44.3
	Geometric Mean[1]	NA	0.684
	Median	NA	0.773
	Minimum, Maximum	NA	0.258, 1.28

$AUC_{0\text{-}tau}$ = area under the concentration-time curve from time zero (predose) through 24 hours; $AUC_{0\text{-}tldc}$ = area under the concentration-time curve from time zero (predose) to the time of last determinable concentration; C_{24} = plasma minocycline concentration 24 hours after FMX103 1.5% application; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; NA = not applicable; PK = pharmacokinetic; R_{ACC} = accumulation ratio; T_{max} = time to maximum measured plasma concentration

Source: 8 in 2.7.2 Summary of clinical pharmacology studies

14.4.2. Summary of Bioanalytical Method Validation and Performance

Plasma minocycline concentrations were determined using chromatographic separation on a C8 column using gradient conditions with liquid chromatography with tandem mass spectrometry detection according to method validation report (N-A-BIO-15-010) by (b) (4). Minocycline and the internal standard, minocycline-d6, were separated from human plasma by protein precipitation. A total of 1309 and 420 plasma samples were collected and analyzed from studies FX2014-03 and FX2017-14, respectively. The assay validation results are summarized in Table 39.

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Table 39: Validation Results of the LC-MS/MS Bioanalytical Methods Used for Measuring Plasma Concentration of Minocycline in Studies FX2017-14 and FX2014-03

Analytes	Minocycline
Matrix	Li-Heparin human plasma
Standard curve assay range	0.257 ng/mL – 205 ng/mL
Intra-run precision (%)	2.0 to 6.2
Intra-run accuracy (%)	-9.4 to 0.1
Inter-run precision (%)	2.2 to 11.9
Inter-run accuracy (%)	-8.4 to 0.0
Freeze/thaw matrix stability	3 cycles at -20°C and -70°C
Room temperature stability	24 hours
Processed-sample viability	72 hours at 10℃ and refrigerated (5℃ ±3℃)
Long term stability	80 days at -20°C; 184 days at -75°C (the study samples were stored at -20°C and the maximum sample storage time was 60 days)
Incurred sample reanalysis	FX2017-14: a total of 44 out 420 samples (10% of study samples) were re-analyzed and 40 samples (90.9%) were within the defined acceptance criteria (i.e., difference within ±20% of average of original and repeat value for at least 2/3 of the samples). FX2014-03: Incurred sample reanalysis was performed in a total of 116 samples (8.9% of study samples) and 108 samples (93.1%) met the prespecified criteria.

Abbreviation: Liquid chromatography–mass spectrometry/mass spectrometry

14.5. Clinical/Biostatistics

Table 40: Demographic Characteristics of the Phase 2/3 Safety Population

Characteristic	Minocycline Foam 1.5% (n=1087)	Vehicle Foam (n=591)	Totals n=1678
Age - mean and std.dev.	49.92 [13.92]	50.88 [13.37]	50.26 [13.73]
Age - median	50	51	50
Age – range	18-85	18-86	18-86
Age Range 40-65, count subjects and %			
<40	265 (24.4%)	117 (19.8%)	1018 (60.7%)
40-64	650 (59.8%)	368 (62.3%)	382 (22.8%)
≥65	172 (15.8%)	106 (17.9%)	278 (16.6%)
Sex - count subjects and %			
F	772 (71.0%)	395 (66.8%)	1167 (69.5%)
M	315 (29.0%)	196 (33.2%)	511 (30.5%)
Race - count subjects and %			
White	1050 (96.6%)	569 (96.3%)	1619 (96.5%)
Asian	11 (1.0%)	8 (1.4%)	19 (1.1%)
Black or African American	14 (1.3%)	5 (0.8%)	19 (1.1%)
Native Hawaiian or Other Pacific Islander	3 (0.3%)	4 (0.7%)	7 (0.4%)
American Indian or Alaska Native	3 (0.3%)	2 (0.3%)	5 (0.3%)
Multiple	4 (0.4%)	1 (0.2%)	5 (0.3%)
(Missing)	1 (0.1%)	2 (0.3%)	3 (0.2%)
Other	1 (0.1%)	0 (0.0%)	1 (0.1%)

Source: Reviewer's Table created in JReview using Applicant's datasets

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Note: The Phase 2 trial was conducted in Germany; the ethnicity of subjects was not reported. Ethnicity information for the Phase 3 trials is presented in the table below:

Table 41: Subject Ethnicity in the Phase 3 Trials

Ethnicity	Minocycline Foam, 1.5% (n=1008)	Vehicle Foam (n=513)
Not Hispanic or Latino	676 (67.1%)	339 (66.1%)
Hispanic or Latino	330 (32.7%)	174 (33.9%)
Missing	2 (0.2%)	0 (0.0%)

Source: Reviewer's Table created in JReview using Applicant's datasets

Narrative summaries of subjects treated with minocycline foam, 1.5% who experienced SAEs:

Trial FX2015-10

A 60 y/o female (Subject (b) (6)) was noted at Screening on 12/11/2015 to have moderate bruising of the head secondary to a fall on (b) (6). She was hospitalized on (b) (6) and discharged on (b) (6). The action taken with study drug was reported as not applicable as the subject had not yet received any study drug. The event was reported as recovered in Dec 2015. The investigator assessed the AE of contusion as serious (hospitalization), moderate in severity, and unrelated to study drug administration.

A 75 y/o male (Subject (b) (6)) was randomized to minocycline foam, 1.5% on 11/16/2015 and used the last dose of study drug on 2/2/2016. The subject had a medical history remarkable for hypercholesterolemia, diabetes mellitus, arterial hypertension, obesity, and ulcerative colitis. On (b) (6), the subject experienced SAE of cerebral hemorrhage, pulmonary embolism, and hemiparesis. He was hospitalized in the intensive care unit from (b) (6). At the time of the clinical study report, the events were ongoing. The investigator assessed the cerebral hemorrhage, pulmonary embolism, and hemiparesis as serious (hospitalization), severe, and unrelated to study drug administration.

Trial FX2016-11

A 63 y/o female (Subject (b) (6)) was treated with minocycline foam, 1.5% beginning (b) (6). She had an extensive past medical history. Relevant history included hypertension, hyperlipidemia, and diabetes (since 1994), migraines (since 1998), coronary artery bypass graft (January 2008), coronary artery disease (since 2008), and ST segment elevation with myocardial infarction. Relevant concomitant medications included nitroglycerin, metformin, carvedilol, gabapentin, losartan, colestipol, insulin aspart, ticagrelor, topiramate, and cyclobenzaprine. On (b) (6), she experienced chest palpitations and shortness of breath along with dizziness on standing and was evaluated on the emergency department. ECG and troponins were both within normal limits. The subject was admitted to the telemetry unit of the hospital for monitoring. She was discharged from the hospital on (b) (6). The SAE of syncope was considered resolved on (b) (6). No action was taken with the study drug, and the subject completed the study. Other AEs reported for this subject included palpitations from (b) (6) to

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(b) (6) (Days 24-29). The palpitations were considered to be mild in severity and unlikely related to the study drug. The investigator noted the severity of this event of syncope as moderate, the outcome as resolved, and the relationship to study drug as unlikely.

A 51 y/o female (Subject (b) (6)) began treatment with minocycline foam, 1.5% on (b) (6). Her medical history was remarkable for eczema, seasonal allergies (since 1980), dry cough, obesity (since 2008), anemia, dizziness, and hypertension (since 2016). On (b) (6) (Day 11), the subject presented at the emergency department with complaints of shortness of breath associated with nausea, fatigue, and chest discomfort that felt like tightness that radiated to her upper back. The subject denied having fever, chills, headache, or dizziness. ECG was normal and troponin and stress test were negative. She was given intravenous fluids for possible dehydration and admitted overnight for observation. The dyspnea and dehydration resolved. On (b) (6) (Day 12), ondansetron, acetaminophen, nitro ointment, and nitroglycerin were administered for 1 day. She was also administered aspirin, famotidine, and fluticasone and instructed to continue these medications after discharge. No action was taken with the study drug, and she received her last dose on (b) (6) (Day 70). On (b) (6) (Day 12), the SAE of nausea, chest pressure, fatigue, dehydration, and shortness of breath were considered resolved. The event of flare up of seasonal allergies was ongoing. The investigator considered all of the events to be mild in severity and unlikely related to the study drug.

Trial FX2016-12

A 66 y/o female (Subject (b) (6)) with a history of hypertension treated with losartan began treatment with minocycline foam, 1.5% on (b) (6). On (b) (6), she experienced "pressure on her chest" and presented to the emergency department. ECG, echocardiogram, chest X-ray, and a coronary computed tomography (CT) angiogram were negative. Her blood pressure was noted to be elevated with systolic readings in the 180s and she was admitted for further evaluation and treatment. The subject was started on carvedilol, amlodipine, and pravastatin, and her losartan was discontinued. On (b) (6) (Day 16), she was discharged from the hospital in stable condition and the SAE of uncontrolled hypertension was considered resolved. The investigator considered the severity of the SAE of uncontrolled hypertension as mild, the outcome as resolved, and the relationship to study drug as unlikely.

Trial FX2016-13

A 62 y/o female (Subject (b) (6)) with history remarkable for diabetes mellitus (since Oct 1999) and hypertension (since 2010) began treatment with minocycline foam, 1.5% on (b) (6). She was admitted to the hospital for pneumonia on (b) (6) (Day 110) and was treated with IV levofloxacin. She was discharged on (b) (6) (Day 115) and the SAE of pneumonia was considered resolved the same day. The action taken with the study drug was drug interrupted. The subject applied her last dose on (b) (6) (Day 160) and withdrew her consent on (b) (6) (Day 213). The investigator considered the severity of the event of pneumonia as severe, the outcome as resolved, and the relationship to the study drug as unlikely.

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A 25 y/o female (Subject (b) (6)) with an unremarkable past medical history began treatment with minocycline foam, 1.5% on (b) (6). She underwent an endometrial biopsy on (b) (6) (Day 289) and had a post-endometrial biopsy hemorrhage. She was admitted to the intensive care unit and required a blood transfusion. On (b) (6) (Day 290), she was discharged from the hospital and the SAE of post-procedural hemorrhage was considered resolved. Action taken with the study drug as a result of this event was drug interrupted. She applied her final dose of study drug (b) (6) (Day 301). The investigator considered the severity of the event of post-procedural hemorrhage as severe, the outcome as resolved, and the relationship to the study drug as unlikely.

A 46 y/o female (Subject (b) (6)) with an unremarkable past medical history began treatment with minocycline foam, 1.5% on (b) (6). She underwent a mole removal from her chest on (b) (6) which was revealed to be melanoma. She underwent excision (b) (6), and the SAE of melanoma was considered resolved on this date. Other non-serious AEs reported for this subject while she was receiving treatment included actinic keratosis. The investigator considered the severity of the event of malignant melanoma as severe, the outcome as resolved, and the relationship to the study drug as unlikely.

A 34 y/o male (Subject (b) (6)) with a history of hypercholesterolemia, type 2 diabetes, and hypertension began treatment with minocycline foam, 1.5% on (b) (6). The subject had reported spontaneous CSF leak beginning in (b) (6), and subdural hematoma was diagnosed on CT scan on (b) (6) (Day 107). He was hospitalized on (b) (6) (Day 110) with bilateral subdural hematomas and CSF leak. The CSF leak was patched on (b) (6) (Day 123); the bilateral hematomas were drained on (b) (6) (Day 127). The events were considered resolved on (b) (6) (Day 131). Although the Applicant reported that no action with the study drug was taken as a result of these events, the subject applied his last dose on (b) (6) (Day 101) and the subject withdrew consent and discontinued on (b) (6). The investigator considered the severity of the events of subdural hematoma and cerebrospinal fluid leakage as moderate, the outcome as resolved, and the relationship to the study drug as unlikely.

A 49 y/o female (Subject (b) (6)) with a history remarkable for caesarean sections (13 Nov 2003, 12 Aug 2008, and 14 Feb 2012), gastric bypass surgery (date not provided) and abdominal hernia (since 2012) began treatment with minocycline foam, 1.5% on (b) (6). On (b) (6) (Day 180), she presented to the emergency department with mild epigastric abdominal pain without vomiting. On (b) (6) (Day 181), an abdominal CT scan showed multiple umbilical and supra-umbilical hernias, one of which contained transverse colon without evidence of strangulation or obstruction. She was diagnosed with colonic entrapment, which resolved spontaneously with simethicone. On (b) (6) (Day 183), she was discharged from the hospital and the event was considered resolved. No action was taken with the study drug as a result of this event; she applied her final dose on (b) (6) (Day 279). The investigator considered the severity of the event of large intestinal obstruction as moderate, the outcome as resolved, and the relationship to the study drug as unlikely.

A 62 y/o female (Subject (b) (6)) with relevant past medical history of angina pectoris (since 1980), chronic obstructive pulmonary disease (COPD) and hypertension (both since 2000)

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began treatment with minocycline foam, 1.5% on (b) (6). On (b) (6) (Day 19), she began to experience cough, wheezing, shortness of breath, and fatigue. She was admitted to the hospital for worsening of COPD from (b) (6) (Days 19-23). Her condition was improved at the time of discharge. The action taken with the study drug as a result of this event was drug interrupted on (b) (6) (Day 19). The study drug was restarted on (b) (6) (Day 24). The investigator considered the severity of the event of COPD as severe, the outcome as resolved, and the relationship to the study drug as unlikely.

A 63 y/o female (Subject (b) (6)) with relevant past medical history of depression, hyperlipidemia, obesity, and anxiety. On (b) (6) (Day 179), the subject was admitted to the hospital for observation after experiencing syncope. A CT scan of the head, chest x-ray, and overnight observation for arrhythmia on the telemetry unit were all negative. She was discharged to home on (b) (6) (Day 180) and the investigator considered the SAE resolved. Action taken with study drug was drug interrupted. The subject reported that she was unable to bring her medication kits to the hospital and therefore missed the dose on (b) (6) and (b) (6) (Days 179-180). The study drug was restarted on (b) (6) (Day 181). The investigator considered the severity of the SAE of syncope as moderate, the outcome as resolved, and the relationship to the study drug as unlikely, and suggested a possible etiology of anxiety.

A 75 y/o male (Subject (b) (6)) with a non-contributory past medical history experienced periorbital cellulitis above the left eye beginning on (b) (6) (Day 200). He was initially treated as an outpatient with sulfamethoxazole/trimethoprim. However, his condition worsened, and he was admitted to the hospital for periorbital cellulitis of the left eye and staphylococcal infection (presumptive Methicillin-resistant Staphylococcus aureus [MRSA]). He was treated with IV vancomycin from (b) (6) (Day 202-204). On (b) (6), he received an infusion of dalbavancin as an outpatient. The action taken with study drug was drug interrupted. The investigators considered the severity of the events of periorbital cellulitis and Staphylococcal infection as severe, the outcome as resolved, and the relationship to the study drug as unlikely.

A 60 y/o male (Subject (b) (6)) with relevant past medical history of tinnitus, chronic sinusitis, and allergic rhinitis presented to the emergency department with benign paroxysmal vertigo, nausea, and vomiting on (b) (6) (Day 211). His blood pressure upon arrival was 208/107 mmHg but improved to 156/92 mmHg during evaluation. The subject was admitted to the hospital and started on IV fluids, meclizine, and steroids. A CT scan of the head was normal on (b) (6) (Day 212). He improved and was discharged on (b) (6) (Day 213). No action was taken with the study drug. The investigator considered the severity of the event of labyrinthitis as severe, the outcome as resolved, and the relationship to the study drug as unlikely, and suggested an alternative etiology of infection/virus.

A 53 y/o male (Subject (b) (6)) with a non-contributory past medical history experienced blurred vision beginning (b) (6) (Day 12). On (b) (6) (Day 17), MRI results revealed subacute posterior circulation infarcts involving the right cerebellar hemisphere and vermis without evidence of hemorrhagic transformation or mass effect. The magnetic resonance angiogram (MRA) was negative with no focal vascular occlusion to explain the right cerebellar

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infarct. On (b) (6), the blurred vision recurred, and he was admitted to the hospital for a repeat MRI and MRA. The MRI results showed evolving subacute infarcts of the right cerebellar hemisphere and vermis but no new infarct or intracranial abnormality. The MRA was normal. On (b) (6), the subject was discharged to home in stable condition, and the following day the event was considered resolved. No action was taken with the study drug. The other non-serious adverse event reported for this subject that coincided with the cerebrovascular accident was hypertension, which was considered moderate in severity, unlikely related to the study drug, and resolved. The investigator considered the severity of the event of cerebrovascular accident as moderate, the outcome as resolved, and the relationship to the study drug as unlikely, and suggested an alternative etiology of idiopathic.

A 46 y/o female (Subject (b) (6)) with a past medical history remarkable for nephrolithiasis and treatment with hydrochlorothiazide presented to the emergency department with complaints of chest pressure and palpitations on (b) (6) (Day 305). Her potassium level was 3.3 mmol/L (normal range 3.5-5.1 mmol/L). She was admitted to the telemetry unit for further evaluation and received potassium replacement because the palpitations were considered to be likely secondary to low potassium levels. Her potassium level was 3.5 mmol/L and she was discharged from the hospital on (b) (6) (Day 306). No action was taken with the study drug as a result of this event. The investigator considered the severity of hypokalemia as moderate, the outcome as resolved, and the relationship to the study drug as unlikely, and suggested an alternative etiology of concomitant medication with hydrochlorothiazide.

A 47 y/o female (Subject (b) (6)) with a non-contributory past medical history experienced abdominal pain, fever, and chills beginning (b) (6) (Day 55). On (b) (6), she presented to the hospital with perforated appendicitis with secondary sepsis, leukocytosis, and anemia. She underwent a laparoscopic appendectomy and was treated with IV antibiotics. On (b) (6) (Day 68). Action taken with the study drug as a result of this event was permanent discontinuation on (b) (6) (Day 62). The investigator considered the severity of perforated appendicitis as severe, the outcome as resolved, and the relationship to the study drug as unlikely, and suggested an alternative etiology of infection.

Narratives of subjects who discontinued because of AEs in the Phase 2/3 safety population and long-term extension Study FX2016-13 are presented below:

<u>FX2016-11</u>

A 39 y/o male (Subject (b) (6)) with a past medical history remarkable for acne experienced a cyst on his nose on (b) (6) (Day 48). The cyst resolved on (b) (6) (Day 50) and he was discontinued from the study because of this event on (b) (6) (Day 57). The investigator considered the severity of the event as mild, the outcome as resolved, and the relationship to study drug as unlikely.

A 64 y/o female (Subject (b) (6)) with a non-contributory past medical history experienced influenza on (b) (6) (Day 50). Her last dose of study drug was (b) (6) (Day 53). She was discontinued from the study for this event on (b) (6) (Day 86). The investigator considered

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the severity of the event as mild, the outcome as resolved, and the relationship to the study drug as unlikely.

A 65 y/o female (Subject (b) (6)) with a non-contributory past medical history experienced a UTI on 6/22/2017 (Day 4). Her last dose of study drug was 6/25/2017 (Day 7). The UTI resolved on 6/27/2017 (Day 9) and she was discontinued from the study for this event the same day. The investigator considered the severity of the event as mild, the outcome as resolved, and the relationship to study drug as unlikely.

An 81 y/o male (Subject (b) (6)) with a non-contributory past medical history experienced AEs of inflamed dermatitis and pruritus on his back on 9/11/2017 (Day 20) which resolved 10/4/2017 (Day 43). His last dose of study drug was 9/14/2017 (Day 23) and he was discontinued from the study for these events on 10/20/20017 (Day 59). The investigator considered the severity of the events as moderate, the outcome as resolved, and the relationship to study drug as unlikely.

A 63 y/o female (Subject (b) (6)) with a non-contributory past medical history experienced a bladder mass on (b) (6) (Day 47) which resolved on (b) (6) (Day 68). Her last dose of study drug was (b) (6) (Day 57). She was discontinued from the study for this event on (b) (6) (Day 97). No further information was provided regarding treatment of the mass. The investigator considered the severity of the event as moderate, the outcome as resolved, and the relationship to study drug as unlikely.

<u>FX2016-12</u>

A 44 y/o female (Subject (b) (6)) with an unremarkable past medical history experienced telangiectasia on 7/26/2017 (Day 1), prior to the first application of study drug (i.e. the AE was not treatment-emergent). Dosing with the study drug continued until 8/2/2017 (Day 8). The event of telangiectasia resolved, and the subject was discontinued from the study on 8/9/2017 (Day 15). The Investigator considered the severity of the event as mild, the outcome as resolved, and the relationship to study drug as unlikely.

A 66 y/o male (Subject (b) (6)) with a non-contributory past medical history experienced pruritus on 3/13/2018 (Day 2). Dosing with the study drug continued until 3/18/2018 (Day 7). The pruritus resolved on 3/20/2018 (Day 9). He was discontinued from the study for this event on 4/16/2018 (Day 36). The Investigator considered the severity of the event as moderate, the outcome as resolved, and the relationship to study drug as probable.

<u>FX2016-13</u>

A 49 y/o female (Subject (b) (6)) with an unremarkable past medical history experienced mydriasis in the left pupil on 12/22/2017 (Day 33). Dosing with the study drug continued until 1/20/2018 (Day 62). She was discontinued from the study for this event on 2/19/2018 (Day 92). The Investigator considered the severity of the event of mydriasis as moderate, the outcome as not resolved, and the relationship to the study drug as possible.

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A 37 y/o female (Subject (b) (6)) with an unremarkable past medical history experienced enchondromatosis of the femur on 12/27/2017 (Day 71). Dosing with the study drug continued until 1/8/2018 (Day 83). She was discontinued from the study for this event on 4/3/2018 (Day 168). The Investigator noted the severity of the event of enchondromatosis as mild, the outcome as not resolved, and the relationship to the study drug as unlikely.

A 37 y/o female (Subject (b) (6)) with an unremarkable past medical history experienced contact dermatitis and was treated with hydrocortisone 1.0% on 3/12/2008 (Day 81). Dosing with the study drug continued until 3/26/2018 (Day 95). She was discontinued from the study for this event on 5/19/2018 (Day 149). The Investigator noted the severity of the event of contact dermatitis as mild, the outcome as resolved, and the relationship to the study drug as possible.

A 64 y/o male (Subject (b) (6)) with an unremarkable past medical history experienced a flare of rosacea on 11/16/2017 (Day 1). Dosing with the study drug continued until 11/30/2017 (Day 15). The rosacea was considered resolved on 12/13/2017 (Day 28). He was discontinued from the study for this event on 8/27/2018 (Day 285). Other non-serious adverse events reported for this subject while he was receiving treatment included erythema and pruritus of the face, which started the same day as the rosacea. The investigator considered the erythema to be moderate and the pruritus to be severe and considered both to be probably related to study drug. The investigator considered the event of rosacea as moderate, the outcome as resolved, and the relationship to study drug as probable.

14.6. Additional Clinical Outcome Assessment Analyses

This section is not applicable.

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/s/

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